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RELATION OF RECOVERY OF SENSATION TO INTRASPINAL PATHWAYS IN INJURIES OF THE SPINAL CORD

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CHICAGO

THE MATERIAL which we have studied consists of 60 cases of injuries to the spinal cord in which sensory recovery was taking place and in which sensory examinations had been made several times, the last one in 1952.

No attempt was made to examine for sensory recovery by tests other than those used in an ordinary neurological examination. Two-point discrimination was not studied, and neither an algesiometer nor an esthesiometer was used. Some of the cases had been described in the study of Boshes, Brown, and Crouch,[1] but for the most part these cases have not been reported.

Many studies have been made upon recovery of sensation after injury to the spinal cord in an attempt to discover the intraspinal pathways for sensations of different modalities and the form and position of dermatomes, and we have fallen into the same trap.

Read at the Seventy-Seventh Annual Meeting of the American Neurological Association, Atlantic City, N. J., May 9, 1952.

From the Department of Nervous and Mental Diseases, Northwestern University Medical School, and the Neurological Division, Veterans Administration Hospital, Hines, Ill.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Boshes, B.; Brown, M., and Crouch, R. L.: Sensory Return in Partial and Recovery Spinal Cord Lesions, Neurology **2**:81, 1952.

Although it will be seen that we have not been able fully to predict what anatomical studies may later show to be the intraspinal pathways, and other studies, the spinal dermatomes, we have obtained interesting information about the manner of recovery of sensation in these injuries and an indication as to their anatomical and embryological significance.

When the spinal cord is injured by a knife or a part is sectioned by a surgical procedure, the ensuing loss of sensation may, with some degree of accuracy, be used in studying intraspinal pathways of sensation. Even in such a case, unless the patient dies and histological studies are made, there are many pitfalls.

Because of the successful management of the patients with residuals of injuries to the spinal cord, these patients have been, and are being, kept alive for years, and the opportunity to study spinal cords by histological methods is slight indeed. It becomes necessary, therefore, to learn what is possible from clinical studies.

Of course, in a discussion of recovery of sensation after an injury of the spinal cord, it is apparent that such recovery is the result of return of function temporarily abolished not by destruction of fibers but by blocks produced by pressure, anoxia, inflammation, etc. At times, the whole transverse area of the spinal cord may be injured, but not to the degree which produces degeneration of the distal segments of the axons. In such a case of complete transverse injury, recovery occurs rather simultaneously over the body distal to the point of injury, and all modalities of sensation recover together. This situation is rare. Usually one part of the spinal cord is injured more severely than other parts, and the less injured parts recover sensation earlier. Among such cases may be those in which the anterior part of the spinal cord may be more severely injured and the sensory return suggests the pattern of thrombosis of the anterior spinal artery. In cases of another type the medial portion of the spinal cord is less severely injured, and sensory recovery is shown by a dropping downward of the level of sensory loss; in another type the periphery of the spinal cord may be less severely injured and recovery be shown by return of sensation first in the sacral segments and later at higher levels. Still another is that in which one-half the spinal cord is not as severely injured as the other, and sensation returns in a manner that suggests a Brown-Séquard lesion. In many cases the spinal cord is injured severely only in patches, and sensory recovery in small patches suggests such a lesion. Finally, the residual loss of sensation may occupy an area which represents a region of an extremity, such as below the lower third of the leg and foot, and have a stocking-like type of distribution, rather than that of an anatomical dermatome.

Although the sensory dermatomes have been described in respect to the radicular supply of sensation to the skin, the border of sensory loss following injury to the spinal cord alone has not been successfully ascertained. The reason for this is found in the fact that when the cervical portion of the spinal cord is injured, there frequently occurs a simultaneous injury to the cervical roots or brachial plexus or both. This is also the situation in regard to injury to the lumbar portion of the spinal cord, where injury may also occur to roots in the cauda equina. Therefore, we have studied the sensory changes in the trunk and lower extremities in patients with lesions of the cervical and thoracic portions of the spinal cord. This would permit delineating the dermatomes only of the trunk and the lower extremities.

When recovery began in the uppermost border of sensory loss in the trunk and descended to include parts of the lower extremities, it could not be held that the

upper border of the residual sensory loss represented a border of a dermatome. In such a case, fibers adjacent to other consecutive ones may overlap, and one may observe parts of skin recovering which may represent a fraction of an area of an adjacent upper or lower dermatome. The same is true when recovery begins in the lowermost sacral area and ascends. It is for this reason that from observations, restricted as they were to recovery and residual loss of sensation, we were unable to delineate borders which corresponded either to radicular dermatomes or to levels observed by others when sensory loss resulted from a complete lesion.

What, then, could be studied in our material? We first attempted a correlation between the area of sensory recovery and, with the assistance of motor examination, the part of the spinal cord which was more severely injured. This led to the surprising conclusion that in almost one-half our cases the sensory disturbances resembled those of thrombosis of the anterior spinal artery. A study of cases of sensory recovery from above downward showed a relative restriction of residual loss of sensation to the postaxial surface of the lower extremity, and in cases of recovery from below upward the relative restriction of return of sensation to the same area was found.

It soon became obvious that recovery takes place by the successive recovery of one area of skin adjacent to another and that parts of a number of dermatomes could be included in such an area of recovery. Among these were the combinations of simultaneous return of sensation to the dorsal surface of the trunk and buttocks, or to the anterior thigh and buttocks, and the frequent return of sensation to the genitalia when other parts of the sacral segments were not recovering. We studied recovery of sensation in patches and regional loss of sensation, but not in the form of dermatomes. Finally, by means of a diagram of the sensory tracts in the spinal cord, we studied their lamellar arrangement. We shall devote a small section to each of these.

INJURY TO THE ANTERIOR PORTION OF THE SPINAL CORD

One of the aforementioned, to us surprising and not previously recognized, observations was the large number of cases in which a lesion resembling one produced by thrombosis of the anterior spinal artery was suggested. In 29 of 60 cases, this resemblance was observed, in part or whole. Of these 29, there were lesions in the cervical portion of the spinal cord, all due to fracture dislocation in 21, and in 8 the lesions were in the thoracic portion, 4 of which were due to fracture dislocation, 3 to gunshot wounds, and 1 to a stab wound.

The softening of the spinal cord resulting from thrombosis of the anterior spinal artery affects the pyramidal tract, the lateral spinothalamic tract, and the other tracts of the anterolateral column. Theoretically, it should result in spastic paralysis, loss of pain and temperature senses, and conservation of touch, position, and vibration sensibility. However, in reports of the clinical picture produced by thrombosis of the anterior spinal artery, strict adherence to such a pattern is not constant, and cases are reported in which there were loss of position sense and loss of touch sense in parts of the body. The constant findings are spastic paraplegia and loss of pain and temperature sensations. However, tactile anesthesia is not frequently observed and is generally of slighter degree, if partly lost.

There were 29 cases in which tactile sense was recovering over one-half or the whole of the body. Of these, there were 21 in which the recovery was occurring

over both sides of the trunk and limbs; of these 21, there was but little return of other sensations in 13; some return of pain sense on both sides in 2, and some return of pain sense in one side in 2; in the 8 other cases recovery of pain and temperature senses was also occurring on one side of the body. In six cases the residual sensibility resembled a Brown-Séquard lesion except that touch sense was also recovering on the side on which temperature and pain senses were recovering. Of these six cases, four were of injuries to the cervical, and two of injuries to the thoracic, portion of the cord. In two cases touch sense only was recovering on one side.

In the 13 cases with loss of pain and temperature senses and only diminished tactile sense the condition resembled thrombosis of the anterior spinal artery very closely, and in 5 of them vibration sense was intact (Fig. 1*A*).

Of the eight cases in which pain and temperature senses were recovering on one side and touch sense was recovering on both sides, it is suggested that the lesion constituted a Brown-Séquard type. However, since in so many other cases the sensory loss resembled that of an injury chiefly to the anterior portion of the spinal cord, it appears to us that in those eight cases recovery was occurring in one-half the previously bilateral injury to the anterior portion of the spinal cord. Therefore, touch sense having been but partly affected, all sensations seem to be recovering on one side (Fig. 1*B*).

In six cases touch, pain, and temperature senses were all recovering on one side of the body; in all cases the motor recovery was greater on the opposite side. This has often been described, especially in lesions of the cervical portion of the spinal cord, and the injury in such cases has been classified as the Brown-Séquard type. The observation that touch sense, as well as pain and temperature senses, recovers on the same side has been attributed to the fact that by the time fibers conveying tactile impulses have reached the cervical portion of the spinal cord they will have crossed to the opposite side (Fig. 1*C*).

This may well be the case, but confirmation must await histological study, since when touch sense is recovering on both sides the condition may be interpreted differently. In the case of a thoracic lesion due to a stab wound, with absence of vibration sense on the more severely injured side, the paralysis was definitely of the Brown-Séquard type.

RECOVERY OF SENSATION FROM ABOVE AND FROM BELOW

In some cases, the medial part of the spinal cord seems to be the less injured, and recovery of cutaneous sensation proceeds from above downward. The upper border of the residual loss of sensation may be found at various lower regions of the lower extremities; it does not, however, coincide with previously described radicular or spinal borders. Rather, it is related to the regions of the lower extremities—upper thigh, below the knee, etc.—whatever else may show recovery of sensation; rarely is it observed in the postaxial surface of the extremities (Fig. 2*A*).

The reverse of this may be seen in the cases in which the less severely injured portion of the spinal cord is the periphery and the recovery of sensation is taking place from below upward. In these cases the separate representation of the postaxial surface is even more emphasized. The areas which are recovering are almost exclusively those of the postaxial surface. Whereas in the cases of recovery from above return of sensation might be seen over the anterior portion of thigh and legs,

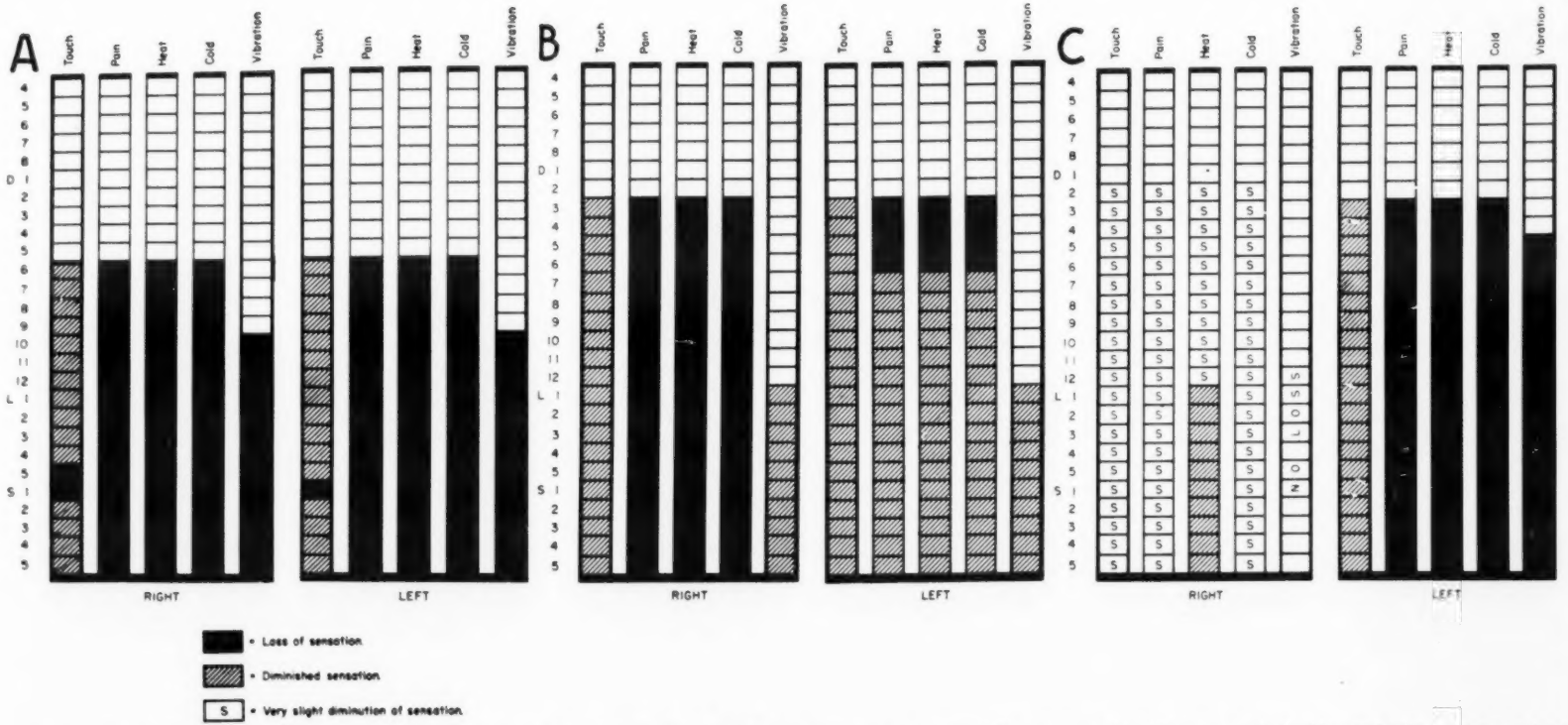

Fig. 1.—Mosaic illustrating (*A*) recovery of touch sense on both sides, but not of pain and temperature senses; (*B*) recovery of tactile sense on both sides, and pain and temperature senses on one side; (*C*) recovery of touch, pain, and temperature senses on one side of the body.

Each block of columns represents a segment of the spinal cord. Each column represents a modality of sensation—pressure, touch, pain, heat, cold, and vibration, respectively.

in the cases of recovery from below upward, these areas rarely show recovery (Fig. 2*B*).

It would appear that there is reluctance in the spread of recovery into the postaxial surface and of spread of recovery from the postaxial surface. This inviolability of the postaxial surface suggests a possible rearrangement in the spinal cord which may be related to its embryological development. It is of interest to refer to the work of Woolsey, Marshall, and Bard.[2] By evoking action potentials, they attempted to map out the representation of cutaneous tactile sensibility in the cerebral cortex of the monkey. They said[2]:

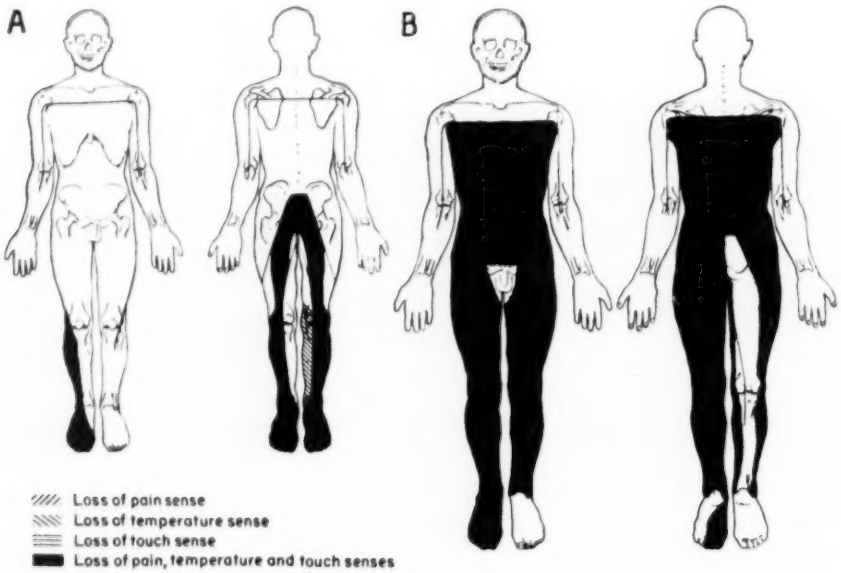

Fig. 2.—*A*, recovery of sensation from above, with persistence of loss of sensation in the postaxial surfaces. *B*, recovery of sensation from below without extension out of the postaxial surfaces.

The features of the cortical representation which we have just emphasized have led us to undertake an analysis of the tactile sensory projection area in terms of spinal cord segments. . . . It can be seen that the spinal segments from the first thoracic (T1) through the last caudal (Ca_1) are projected to the (contralateral) postcentral gyrus and paracentral lobule in the same serial order as that in which they are arranged in the cord. This results in the folowing cortical sequence: . . . the preaxial surface of the leg (thigh, knee, lower leg, anterior aspect of the ankle), toes I-V, postaxial surface of the leg (heel, calf, popliteal fossa, thigh), genitalia, anus, tail.

The authors further stated that the currently accepted sequence "hip, knee, ankle, toes, perineum" must be expanded to take into account the separable representations for preaxial and postaxial surface of the leg.

Our observations seem to support this view for the spinal cord.

2. Woolsey, C. N.; Marshall, W. H., and Bard, P.: Representation of Cutaneous Tactile Sensibility in the Cerebral Cortex of the Monkey as Indicated by Evoked Potentials, Bull. Johns Hopkins Hosp. **70**:399, 1942.

RECOVERY OF BACK AND SADDLE AREA

An exception to the impediment of spread of recovery of sensation into the postaxial surface of the lower extremities is found in cases in which the dorsal, not the ventral, portion of the trunk is regaining sensation. In such cases the recovery of sensation proceeds downward across the junction of the external axial lines and proceeds into the buttocks, the sacrum, and, at times, the back of the thigh. Here, again, a separate representation in the spinal cord is suggested.

A typical segmental spinal nerve grows outward and very soon subdivides into two branches, the posterior and anterior primary divisions. The cutaneous branches (of the posterior branch)

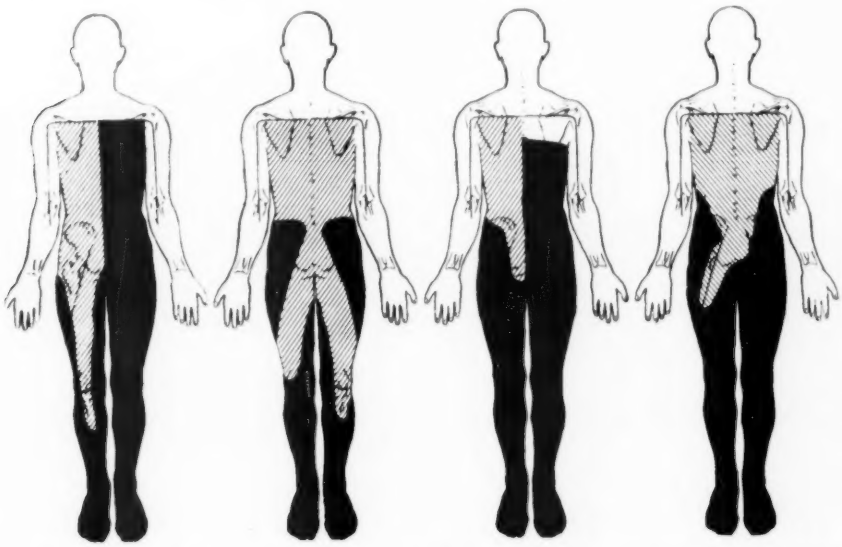

Fig. 3.—Spread of sensory recovery over the back into the postaxial surface of the buttock and thigh. Symbols as in Figure 2.1.

supply strips or segments of skin corresponding roughly to the posterior third of the circumference of the trunk. . . . these cutaneous nerves are concerned also in the innervation of . . . the buttock [Paterson [3]].

The recovery in these cases strongly suggests one that is occurring in the fibers destined to supply the cutaneous area of the posterior primary division of a spinal nerve (Fig. 3). Another interesting instance of recovery of sensation in associated areas is that over the buttocks and anterior surface of the thigh when the residual loss does not suggest any recovery by extension from one dermatome to another. Some of these belong to the group in which recovery is occurring from above downward, including ventral and dorsal surfaces of the trunk, and the recovery is extended on the dorsal surface to the buttock and on the ventral surface to the anterior surface of the thigh (Fig. 4). Of course, the point cannot be proved,

3. Paterson, A. M.: The Anatomy of Peripheral Nerves, London, Oxford University Press, 1919, p. 19.

but in speculating upon the significance of this combination, it is of interest to recall that, because of elongation, angulation, torsion, and pronation of the limb bud, the dorsal surface of the lower limb bud is represented by the front of the thigh and the buttocks, along with the front of the leg and the dorsum of the foot.

DISTRIBUTION OF LOSS OF SENSATION IN REGIONS

Very often, especially when recovery is taking place from above downward, residual loss of sensation is found in a regional part of the extremities. Thus, it may be found in the feet or distal to a portion of the leg or thigh encircling the region and be completely unrelated to dermatomes (Fig. 5). This result of a remote sensory disturbance is reminiscent of the local sensory disturbance described

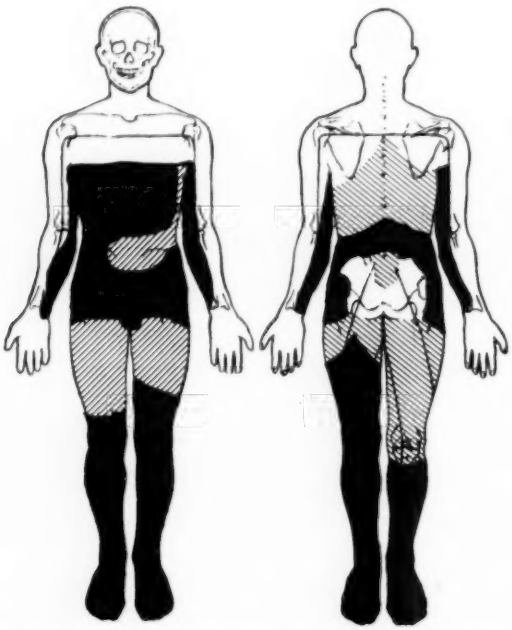

Fig. 4.—Sensory recovery in associated areas over the buttocks and the anterior surface of the thigh. Symbols as in Figure 2*A*.

in the upper extremity by Holmes.[4] In his case, he explained the distribution by an anatomical arrangement of the sensory pathways. The arrangement provided for a sensory supply of part of an extremity which would be related to a segmental reflex. Thus, muscles whose motor supply may be limited to a few roots receive impulses from skin supplied by many more roots. In our cases of remote sensory disturbance, it is more likely that recovery is occurring by a patch which does not extend along the whole of a segmental lamellar bundle and, therefore, does not include the whole of the dermatomes involved.

4. Holmes, G.: The Goulstonian Lectures on Spinal Injuries of Warfare, Brit. M. J. **2**:855, 1915.

PATCHES

In the cases in which the lesion does not correspond to the Brown-Séquard type of recovery of the anterior, medial, or peripheral portion of the cord, recovery of sensation to patches of skin is frequently seen. They represent small areas of relatively less severe injury to the cord and are to be expected, since the cross section of a spinal cord in cases of similarly partial lesions reveals the patchy character of the more severely injured portions.

The patches vary in size and location, often coalesce with other patches, and at times encircle an extremity. Cases of interesting patches may at times be encountered. In one such case three patches occurred, beginning with one in the buttock, one in the thigh, and one in the leg and foot, as though the crests of undulating fibers were recovering and the troughs as yet had not (Fig. 6).

GENITALIA

The frequency of return of sensation to the genitalia has been noted time and again. We can confirm this oft-repeated observation. The explanation, we believe, is suggested by the character of the areas contiguous to the genitalia. During embryonic life, the body is divided in a segmented manner, and from every metamere there is given off a spinal nerve. When branches of such nerves reach the skin and convey sensory impulses from nerve endings, the sensory area constitutes a dermatome. The branches of some of these nerves do not reach the skin, or reach it only in small numbers. The rest remain buried deep. This is particularly true in the case in which the trunk meets the extremities.

> There is a remarkable gap in the numerical sequence of the nerves that supply the ventral axis of the body. All the nerves between the first lumbar and the second sacral fail to reach the mid-ventral line of the trunk.[5]

Therefore, the area of skin of the genitalia at the junction of the internal axial lines is adjacent to the first lumbar, and the area on the inner surface of the thigh, anterior to the internal axial line, is adjacent to the upper part of the third lumbar segment. In addition, there is a direct supply to the genitalia from the sacral nerves.

It would be expected that when recovery advances from below upward and the lower sacral segments are recovering in the perineum, sensation over the genitalia would be recovering (Fig. 7*A*). There should be the same expectation when sensation is recovering from above and has proceeded downward to include the first lumbar segment, even when recovery is not observed in the other sacral segments over the sacrum or the perineum (Fig. 7*B*). Finally, recovery of sensation could ensue when a patch of return occurred in the areas just anterior to the internal axial lines, in the uppermost part of the inner surface of the thigh (Fig. 7*C*).

We have observed a number of such combinations, and to these various ways by which sensation may return to the genitalia may be attributed the many instances in which recovery in this area is observed. However, it is only fair to say that in a very few cases we observed some return of sensation to the genitalia when there was no recovery elsewhere.

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5. Cunningham, D. J.: Cunningham's Textbook of Anatomy, Ed. 9, edited by J. C. Brash and E. B. Jamieson, London, Oxford University Press, 1951, p. 1113.

SEQUENCE OF FIBER TRACTS CARRYING SENSATIONS OF VARIOUS MODALITIES

If one imagines a cross section of the spinal cord the surface of which is composed of pieces of varied colors, each representing a column of fibers, one would look upon

Fig. 5.—Residual sensory loss in recovery from above occupying regional areas, not dermatomes. Symbols as in Figure 2.1.

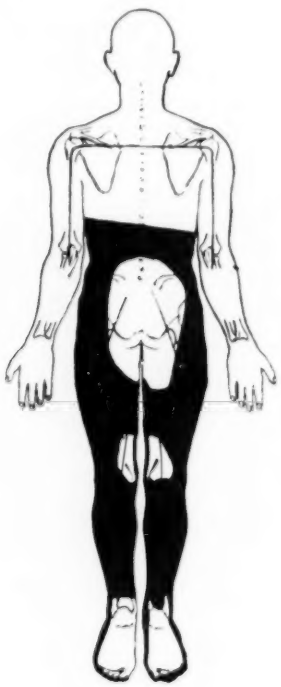

Fig. 6.—Recovery of sensation in patches. Symbols as in Figure 2.1.

it as a mosaic, much as is seen in a cut-out puzzle. The individual pieces, if all were removed and scrambled, could be put together again by the resemblance in color and the reciprocal of shape of one piece to another occupying only a part of a column.

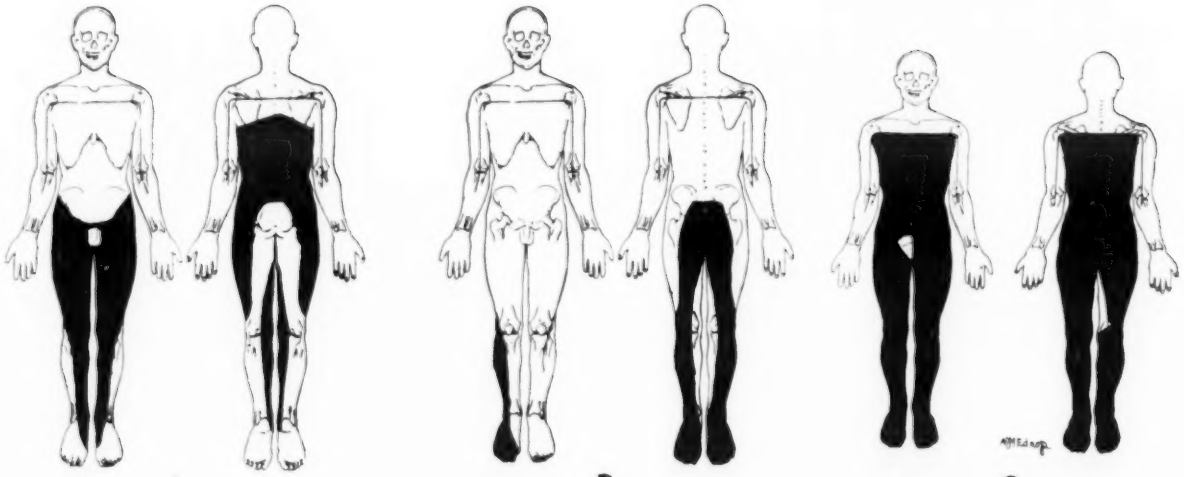

Fig. 7.—Various methods of the recovery of sensation over the genitalia. Symbols as in Figure 2.1.

We have constructed columns of blocks, each representing a segment of the spinal cord. Each column represents a modality of sensation: pressure, touch, pain, heat, cold, and vibration, respectively. We have indicated on each column on every block the state of sensory recovery or loss. The frequency of correlation of the simultaneous recovery in two or more of the modalities of sensation permits one to determine which modality is more likely to be conveyed by fibers adjacent to the other. Particularly valuable are cases in which sensation is recovering in only part of the dermatomes, such as the anterior or posterior surface of the trunk or limbs, or in regions of extremities, or in patches, perhaps in one, at other times in more than one, dermatome.

We have divided the material into two parts: First, cases in which there is a probability that the anterior part of the cord was more severely injured and cases in which the lesion resembled the Brown-Séquard type (constituting 30 cases), and, second, the remaining material of the other types, consisting of 30 cases, 17 of which were of injuries to the cervical cord and 13 of injuries to the thoracic cord. In 10 the lesion was due to gunshot wound, and in 20, to fracture dislocations.

Of the first group, when tactile sense had returned, pressure sense likewise returned in 95%; pain sense was recovering in 54%; cold sense, in 40%, and heat sense, in 35%. When pain sense was recovering, heat sense was recovering in 29.4% and cold sense in 25%. When heat sense was recovering, cold sense was recovering in 100% of the cases. Thus, in this group, it is suggested that the fibers conveying pressure sense are adjacent to those carrying touch sense, that fibers for touch are adjacent to those radiating pain and that temperature fibers are adjacent to those for pain (Fig. 8*A*). Another analysis was conducted somewhat differently. If in the mosaic a small patch in the region occupied by one or more dermatomes was recovering only, with return of touch and pain sense, or pain and cold sense, we should say that in the first case touch was correlated with pain, and in the second, pain with cold (Fig. 8*B*). This led to the following conclusions: Touch sense was correlated with heat sense in 18 cases (31%), with pain sense in 37 cases (63.7%), and with cold sense in 39 cases (67%). A similar analysis made of the other group of cases of recovery from above or below, of regions and patches, consisting of 30 cases, led to the following conclusions: Recovery of touch sense was related to pain sense in 47.8%, to cold sense in 27.5%, and to heat sense in 14.6%. From all the figures, we concluded that the sequence of correlations of sensory recoveries is that of pressure, touch, pain, cold, and heat.

In addition to the comparison of the mosaic columns, we measured the relative sizes of areas of recovery of various modalities of sensation as they appeared in sensory charts. In the first group, since the majority of cases were those in which touch sense was recovering on one or both sides, the largest area of recovery was that of touch sense, in 100%; of the rest, recovery of pain sense was next, then that of cold, and then that of heat.

The same sequence in respect to the relative sizes of areas in which sensations of various modalities—touch, pain, and temperature senses—were recovering was found in the second grouping.

The lamellar configuration of the crossed sensory tracts was well illustrated, and the instances in which heat, cold, pain, and touch sense occupied areas of equal size were rare (Fig. 9).

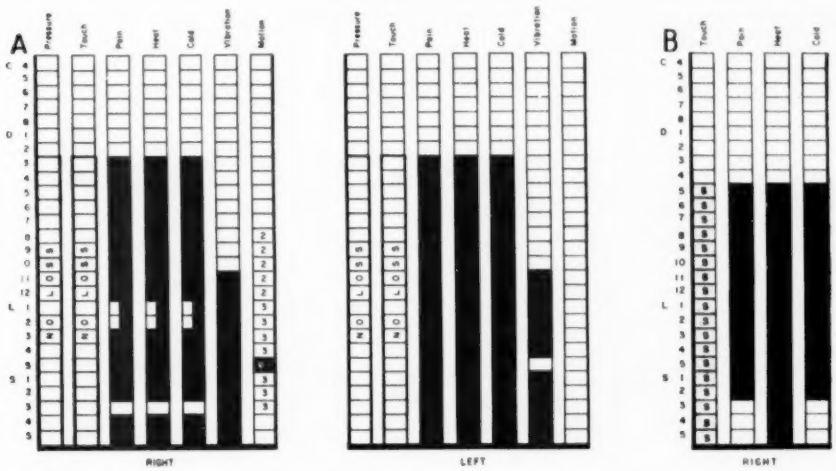

Fig. 8.—*A*, mosaic illustrating concomitant recovery of pressure and touch senses. *B*, mosaic illustrating correlation of recovery of pain and cold senses. Symbols as in Figure 1.

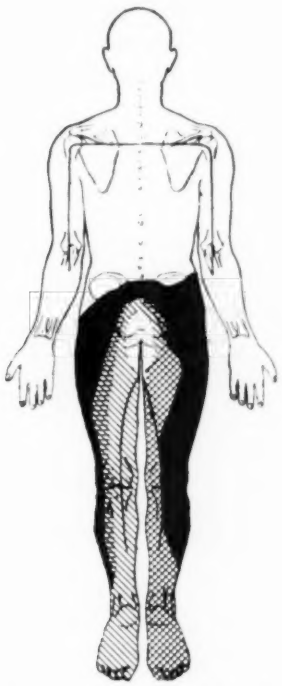

Fig. 9.—Differences in size of areas in which sensation of various modalities is recovering. Symbols as in Figure 2.

Recovery of tactile sensation in the whole or a part of an extremity occurred in 37.3% (83 of 95 extremities); of pain, in 47% (45 of 92 extremities); of cold, in 34% (28 of 88 extremities), and of heat, in 30% (22 of 75 extremities). Vibration sense, for which we were unable to obtain any useful correlations, showed some recovery in 44% (36 of 82 extremities).

Exclusive of the cases in which lesions were severer in the anterior part of the spinal cord and tactile sensation was recovering on one or both sides of the body, recovery of a degree which by clinical methods would be designated as complete occurred in few instances. Occasionally all sensation may have been found to be recovered with the exception of one modality, such as cold, which would be completely lost.

SUMMARY

We point out the necessity of clinical studies alone on return of sensation, since the modern treatment of injuries to the spinal cord has brought about a prolonged longevity of life and few opportunities for histological confirmation of clinical observations.

The reasons for failure to determine the form or sequence of spinal cord dermatomes, in contrast to radicular ones, are described.

By means of a study of diagrams showing loss or recovery of sensation of different modalities, the order of sequence of tracts in the lateral and anterior lateral bundles were seen to be those for pressure, touch, pain, cold, and heat. The largest areas of recovery of various modalities, in descending order, were those for touch, pain, cold, and heat.

In a surprisingly large number of cases recovery of sensation presented the sensory picture of that produced by thrombosis of the anterior spinal artery.

When sensation is recovering from above, there is a reluctance for it to intrude into the postaxial surface of the lower extremity, and when sensation is recovering from below, there is an impediment to extension of recovery beyond the postaxial surface of the lower extremity. This suggests a separate representation in the spinal cord for the preaxial and the postaxial surface of the leg. An exception to this is the simultaneous recovery of the dorsum of the trunk, the buttocks, and the sacrum. This suggests a separate representation of the posterior primary division of the spinal nerves.

The simultaneous recovery of sensation in the anterior surface of the thigh and the buttocks suggests that the association of the thigh and buttocks on the dorsal surface of the limb bud is brought about by various distortions in embryonic life. Attention is called to recovery of sensation in regions, not dermatomes, of extremities, such as the foot, and below the knee, encircling that portion.

Recovery of sensation to the skin of the genitalia occurred when only the upper lumbar segments had recovered, and not the buttocks and sacral segments. It also occurred when the uppermost part of the inner surface of the thigh was recovering and the sacral segments were bereft of sensation. Finally, it occurred with recovery of other sacral segments. These several modes of recovery may be the reason for the high frequency of return of sensation to the genitalia.

MYOCLONUS EPILEPSY AS A SYMPTOM OF DIFFUSE NEURONAL DISEASE

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AND
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UNVERRICHT [1] and Lundborg [2] described a progressive familial syndrome of myoclonus epilepsy, the fully developed form of which was additionally characterized by progressive dementia, pseudobulbar paralysis, rigidity and, in the late stages, quadriplegia in flexion. Diverse types of pathological nerve cell change have been reported to occur in patients with this syndrome,[3] of which an excellent discussion was given by Hodskins and Yakovlev.[3e] The striking feature of these reports is the description of diffuse neuronal disease, either diffuse "primary atrophy" or diffuse cellular changes characterized by cellular inclusions. Though descriptions of myoclonus epilepsy almost always refer to the curious dark-staining

Senior Research Fellow (Clinical Neurology) National Research Council, 1949-1952 (Dr. Watson).

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From the Neurological Unit, Boston City Hospital, and the Department of Neurology, Harvard Medical School.

1. Unverricht, H.: Die Myoclonie, Leipzig, Franz Deuticke, 1891; Über familiäre Myoclonie, Deutsche Ztschr. Nervenh. **7**:32-67, 1895.

2. Lundborg, H.: Die progressive Myoklonus-Epilepsy (Unverricht's Myoklonie), Upsala, Almqvist & Wiskell, 1903.

3. (*a*) Lafora, G. R.: Über das Vorkommen amyloiden Körperchen im Innern der Ganglienzellen, Arch. path. Anat. **205**:295-303, 1911. (*b*) Lafora, G. R., and Glueck, B.: Beitrag zur Histopathologie der myoklonischen Epilepsie, Ztschr. Neurol. u. Psychiat. **6**:1-14, 1911. (*c*) Sioli, F.: Über histologischen Befund bei familiärer Myoklonus-Epilepsie, Arch. Psychiat. **51**:30-39, 1913. (*d*) Dawson, J. R., Jr.: Cellular Inclusions in Cerebral Lesions of Epidemic Encephalitis, Arch. Neurol. & Psychiat. **31**:685-700, 1934. (*e*) Hodskins, M. B., and Yakovlev, P. I.: Anatomico-Clinical Observations on Myoclonus in Epileptics and on Related Symptom Complexes, Am. J. Psychiat. **9**:827-848, 1930. (*f*) van Bogaert, L.; Radermecker, J., and Titeca, J.: Les syndromes myocloniques, Acta neurol. et psychiat. belg. **50**:44-47, 1950. (*g*) Yakovlev, P. I.: A Case of Myoclonus Epilepsy with Atrophy of Brain-Stem and Hallervorden-Spatz Type of Pathologic Change in the Pallidum, Substantia Nigra and Dentate Nucleus, Tr. Am. Neurol. A. **68**:95-100, 1942. (*h*) Denny-Brown, D., and Robertson, E. G.: Observations on Records of Local Epileptic Convulsions, J. Neurol. & Psychopath. **15**:97-136, 1934. (*i*) Sjögren, T.: Die juvenile amaurotische Idiotie: Klinische und Erblichkeitsmedizinische Untersuchungen, Hereditas **14**:197-425, 1931. (*j*) Walter, F. K.: Über familiäre Idiotie, Ztschr. Neurol. u. Psychiat. **40**:349-384, 1918. (*k*) Schob, F.: Zur pathologischen Anatomie der juvenilen Form der amaurotischen Idiotie, ibid. **10**:303-324, 1912. (*l*) Pilotti, G.: Myoclonus, Policlinico (sez. med.) **28**:137-173, 1921. (*m*) Greenfield, J. G., and Holmes, G.: The Histology of Juvenile Amaurotic Idiocy, Brain **48**:183-217, 1925.

"amyloid" inclusions described by Lafora and Glueck,[3b] this type of inclusions appears to be extremely rare. A more frequent finding has been the lipoidal inclusions characteristic of amaurotic familial idiocy.

Juvenile amaurotic familial idiocy has been recognized as a distinct clinical type of lipidosis of the nervous system since the publications of Spielmeyer[4] (1906), Vogt[5] (1909), and Merzbacher[6] (1910). Sjögren[31] pointed out that it is to be distinguished from the infantile form of amaurotic familial idiocy on the basis of the predilection of the former for Jewish families. The infantile and juvenile forms have never been reported to occur in the same family.[7] The appearance of epilepsy in childhood, between the ages of 6 and 12 years, in association with a progressive extrapyramidal type of rigidity, leading to dysarthria and dystonic abnormalities of gait, and ultimately to a state of general flexion contracture of the limbs and body, has often been described in this disease. Sjögren[31] stressed this very characteristic clinical syndrome in his comprehensive survey of 115 cases occurring in 50 Swedish families. Nearly all patients with juvenile amaurotic familial idiocy are reported to have had epileptic seizures. In these descriptions there is frequent mention of sudden jerking of the limbs, particularly on stimulation. Thus, although patients with juvenile amaurotic familial idiocy usually exhibit seizures, dementia, characteristic gait, postures, and terminal state, as well as myoclonus in many cases, few authors have noted that such myoclonic jerking movements bring this familial disease within the clinical definition of myoclonus epilepsy. An exception is Sioli,[3c] who reported the pathological findings of diffuse neuronal lipidosis in a case of Recktenwald's,[8] clinically typical of myoclonus epilepsy. Liebers[9] found similar pathological change in a boy with myoclonus epilepsy of early onset.

In his monograph on progressive myoclonus epilepsy, Lundborg[2] also described sporadic, nonfamilial cases in which a similar symptom complex of less progressive or stationary type was presented. Rabot[10] made a special study of such "sporadic" cases of myoclonus with epilepsy and rigidity. Myoclonus without rigidity or other extrapyramidal disorder is commonly encountered among epileptic patients in the form of occasional, unpredictable, single muscular jerks soon after awakening from sleep. Muskens[11] estimated that over 60% of epileptics may experience this phenomenon at one time or another. Rushton[12] reported a familial incidence of this mild myoclonic phenomenon associated with epilepsy. In one of his cases these

4. Spielmeyer, W.: Über eine besondere Form von familiärer amaurotischer Idiotie, Neurol. Centralbl. **25**:51-55, 1906.

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7. Wyburn-Mason, R.: On Some Anomalous Forms of Amaurotic Idiocy and Their Bearing on the Relationship of Various Types, Brit. J. Ophth. **27**:145-173, and 193-207, 1943.

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9. Liebers, M.: Zur Histopathologie der amaurotischen Idiotie und Myoklonus-Epilepsie, Ztschr. Neurol. u. Psychiat. **111**:465-484, 1927.

10. Rabot, L.: De la myoclonie épileptique, Thesis, Paris, Carre & Naud, 1899.

11. Muskens, L. J. J.: Epilepsy: Comparative Pathogenesis, Symptoms, Treatment, Baltimore, William Wood & Company, 1928.

12. Rushton, J. G.: Myoclonus Epilepsy: Report of 2 Cases, Proc. Staff Meet., Mayo Clin. **19**:391-393, 1944.

jerks had continued for over 10 years, without petit mal or grand mal seizures and without mental deterioration. The brother of Rushton's patient had seizures, myoclonus, and dementia. Wilson [13] described this mild type of "myoclonic-epilepsy" as distinct from the myoclonus epilepsy of Lundborg but concluded that the two syndromes do not differ in any essential feature.

The significance of myoclonus in these disorders has been considerably confused by the prominence of myclonus in association with degeneration of the olivary and dentate nuclei in such conditions as rhythmic glossopalatopharyngeal myoclonus and in the dyssynergia cerebellaris myoclonica of Hunt.[14] In accordance with Krebs [15] and van Bogaert,[3f] these disorders may be classified as asynchronous and asymmetrical twitchings or jerkings in the limbs, associated with pathological changes in the dentate and related nuclei, and rhythmic and symmetrical jerkings particularly related to olivary lesions. Hodskins and Yakovlev [3e] and others have

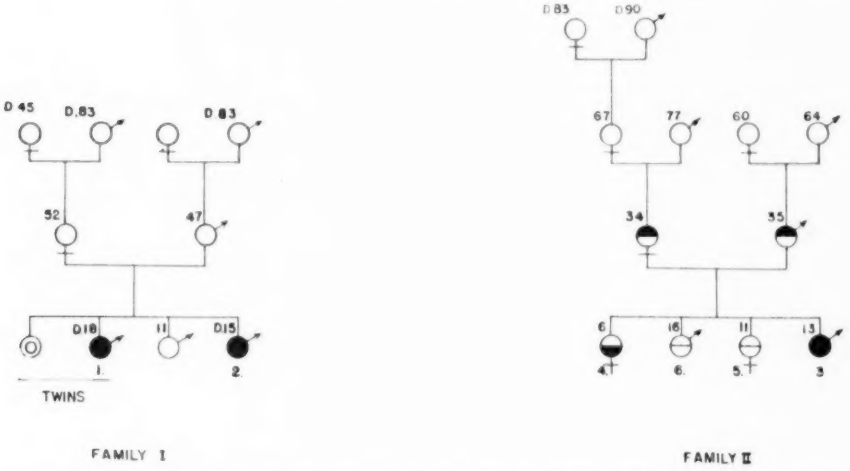

Fig. 1.—Chart of the L. family (Family I) and the P. family (Family II) according to information available in 1952. Cases 1, 2, and 3 and the electroencephalograms in Cases 4, 5, and 6 are described in the text. *D* indicates that the person is dead, and numerals denote the age at death. Unless otherwise indicated, the member is living and well.

Solid black circles indicate myoclonus epilepsy; a circle within a circle means that the child died at birth; clear circles indicate healthy members; clear circles with upper half black, seizures in childhood, and clear circles cut by a horizontal diameter, slight to obvious abnormality of the electroencephalogram but no known seizure.

noted the prominence of cellular lesions in the dentate nuclei in myoclonus epilepsy, though cellular changes in the thalamus and other nuclear masses are also present.

In the large literature which has grown up around this question of the classification of myoclonus, the clinical significance of the peculiar relation between myoclonus and epilepsy appears to have been overlooked.

13. Wilson, S. A. K.: Neurology, edited by A. N. Bruce, Baltimore, Williams & Wilkins Company, 1940.

14. Hunt, J. R.: Dyssynergia Cerebellaris Myoclonica—Primary Atrophy of the Dentate System: A Contribution to the Pathology and Symptomatology of the Cerebellum, Brain **44**: 490-538, 1921.

15. Krebs, É.: Myoclonies et mouvements involontaires de l'encéphalite épidémique, Paris, Gaston Doin & Cie, 1929.

Recent observations on two families presenting myoclonus epilepsy have drawn our attention to the unique features of the symptomatology and offer evidence of its significance as a symptom complex, if not as a disease entity. Diffuse neuronal lipidosis ("cerebromacular degeneration") was demonstrated in one affected member. The second family differed from the first in several important respects, particularly the modified form of attacks in some members, raising questions relevant to the self-limiting seizures of childhood and the larger problem of cryptogenic epilepsy.

CASE HISTORIES AND PATHOLOGY

CASE 1 (Family 1).—J. L., a youth aged 18, was admitted to the Boston City Hospital Jan. 19, 1948, with cough and fever of three weeks' duration, generalized weakness and rigidity of one year's duration, convulsive seizures of eight years' duration, and mental deterioration of nine years' duration.

History.—The parents, grandparents, and great-grandparents were unaffected and were not interrelated. Two of three surviving siblings were affected. One brother, aged 15 years, at the time of this report, was alive and well; the other brother (Case 2) had the same disorder as the patient. The patient was the first-born of premature twins. The first evidence of mental impairment was his failure to progress beyond the third grade in school (normal for age of 8 to 9 years). His first seizures, taking the form of generalized convulsions, occurred at the age of 10 years. He continued to have about two seizures a month despite anticonvulsant medication. An electroencephalogram, recorded in 1945 (at the age of 15), showed abnormal, "spike and slow-wave activity" (Fig. 2). In 1946 the patient was admitted to the Monson State Hospital, Palmer, Mass., because of convulsive seizures and a progressive disorder characterized by "unsteady gait," "slurred speech," mental deterioration, myoclonus, and paraplegia, all of about seven months' duration. One year later (at the age of 17) he was bedridden because of a rigid quadriplegia in flexion and showed myoclonus with movement or sudden stimuli. Thereafter he rapidly lost weight and had onset of fever, cough, and vomiting. He was transferred to the Boston City Hospital.

Physical Examination.—General medical examination revealed emaciation, fever, and evidence of pulmonary consolidation with cavitation. Neurological examination revealed quadriplegia in flexion with resistance to passive movement at all joints. Myoclonus occurred with active and passive motion of the limbs.

Laboratory Findings.—The Hinton reaction of the blood was negative. The cerebrospinal fluid was clear, under pressure of 60 mm. of cerebrospinal fluid, and contained 3 white blood cells per cubic millimeter, one of which was a polymorphonuclear form, and 170 erythrocytes per cubic millimeter. The Pandy reaction was negative for globulin; the total protein was 24 mg. per 100 ml.; the colloidal gold curve was 0012222100. Hinton and Wassermann tests of the cerebrospinal fluid gave negative reactions. Roentgenograms of the chest showed advanced bilateral consolidation with multiple cavitation. Sputum contained acid-fast organisms.

Course.—The patient was treated with bed rest and penicillin. He died Feb. 8, 1948.

Postmortem Examination.—The general findings were those of far advanced pulmonary tuberculosis, with cavitation; miliary tuberculosis, with involvement of the spleen and liver; tuberculous ileocolitis, with involvement of the mesenteric lymph nodes; tuberculous peritonitis, and chronic passive congestion of the liver. Neither the liver nor the spleen was affected by cellular disease.

Brain: (The brain was examined by Dr. Raymond D. Adams, who furnished the pertinent data.) The brain was small, weighing 1,000 gm., with narrow gyri and widened sulci. The meninges were slightly thickened. At the lower end of the left precentral gyrus was a small yellowish focus, in which the cortex was observed to be shrunken, wrinkled, and, on frontal section, destroyed. Frontal section revealed generalized atrophy of both the cortex and the white matter. On microscopic examination the principal abnormality was in the nerve cells, which were unusually round with eccentric nuclei (Fig. 7). The cytoplasm was filled with finely granular material, which displaced the Nissl bodies to the periphery. This inclusion material stained orange-red with oil red O. There were, in addition, considerable loss of nerve cells in all the

parts examined and moderate numbers of microglial cells, some transitional forms, and some phagocytes scattered through the gray masses of the brain. The cerebral cortex, putamen, globus pallidus, thalamus, dentate nucleus, Purkinje cells, and most of the nuclei of the medulla were affected in the manner characteristic of cerebromacular degeneration.

Case 2 (Family I).—R. L., a boy aged 15, was admitted to the neurological service of the Boston City Hospital Dec. 10, 1949, because of convulsions and progressive mental impairment, of five years' duration.

History.—The patient is the brother of J. L. (Case 1), in whom the histopathologic characteristics of neuronal lipidosis were demonstrated. The patient's birth and development were normal until the age of 8 years, when he was placed in a special class because of impaired

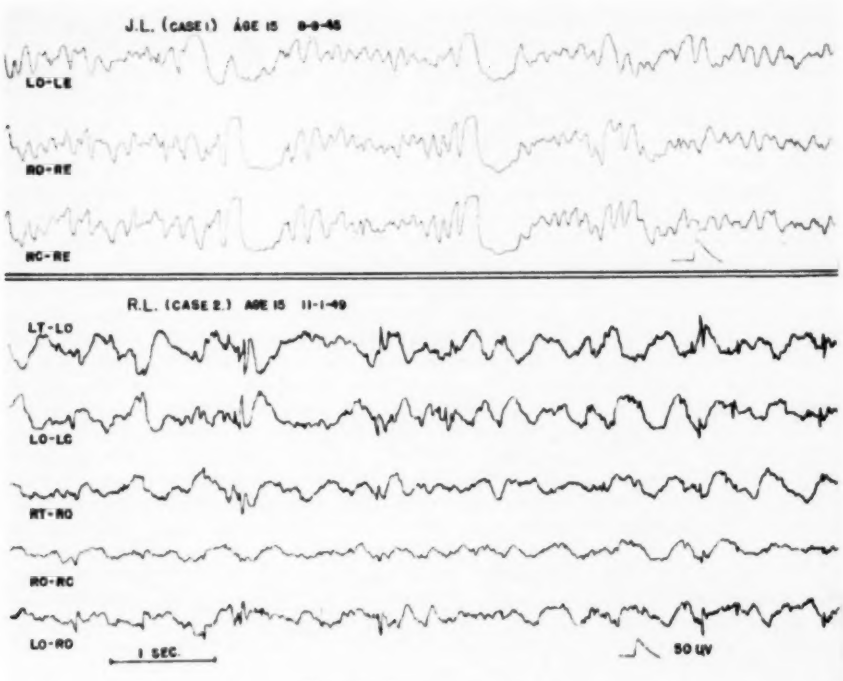

Fig. 2.—Samples of the cerebral electrical activity in Case 1 (J. L.) at the age of 15 years, 6 years after onset of illness, and in Case 2 (R. L.) at the age 15 years, 5 years after onset of illness. *O* means occipital; *C*, central; *T*, temporal; *L*, left, and *R*, right.

concentration, lack of interest in his work, and change in personality. At the age of 9½ years, in June, 1944, he experienced an aura of a "ball of fire," and his first seizure ensued. He fell while walking and lay motionless and unresponsive for five minutes. During the next six months he experienced five seizures, of variable pattern. In one he stared fixedly, became ataxic, and fell, to lie motionless for 15 minutes. In another he experienced a generalized convulsive seizure. Two other seizures began with the head and eyes turning to the left, after which he walked in a circle to the left. Sudden asymmetrical and symmetrical jerking movements of the extremities, preceding the seizures or occurring alone, were noted during the several years preceding admission. The frequency of seizures varied from none to 17 a day, and eventually the attacks were precipitated and influenced in their frequency by passive movement, sound, and light. They occurred on his attempting to stand and during transition states from sleep to the waking state or vice versa. Seizures apparently were unaffected by anticonvulsant medication.

In July, 1946, the patient was admitted to the Massachusetts General Hospital because of seizures. His electroencephalogram showed abnormal, gross symmetrical spike and slow-wave activity. Neither the pneumoencephalogram nor examination of the cerebrospinal fluid revealed changes of significance. Psychometric examination showed a mental age of 8 years, when his chronological age was 11 years 6 months. His intelligence quotient was 70. He was inattentive, worked slowly, and smiled without reason. Memory and reasoning were poor. During 1948, one and one-half years before the final admission, he was bedridden and incontinent, with frequent seizures and progressive rigid quadriplegia. Speech, swallowing, and coughing were greatly impaired. Seizures occurred up to 16 times a day, being precipitated by slight active or passive movement. On one occasion he experienced visual hallucinations. He was admitted to the Boston City Hospital in August because of fever and inability to cough. His speech had been unintelligible for six weeks. The findings on general medical and neurological examinations were not significantly different from those on his final admission, in October, 1949, when he was readmitted because of the failure of anticonvulsant medication to control his seizures.

Examination.—General medical examination showed nothing remarkable. Neither the spleen nor the liver was palpable. The volume of the entire musculature was generally and symmetrically diminished. He spoke only in monosyllabic fragments, which were slurred, weak, and repetitive. He heard, understood, and executed simple oral commands after a variable, but lengthy, delay, e. g., 30 seconds. At rest he lay quiety in a flexed posture, with an impassive facial expression. If disturbed, even by the approach of an unpleasant stimulus he would break into an exaggerated grimace and cry out. He was oriented for time but not for place. Visual acuity and the fundi were normal. Pronounced irregular nystagmus occurred on lateral gaze to either side. There was bilateral facial weakness. The tongue was protruded weakly.

His habitual attitudes when undisturbed was one of flexion at all joints except the ankles, which were in plantar flexion and internal rotation (Fig. 8, upper part). Voluntary movement at any joint was slow and accompanied with irregular clonic movements. Strength was about 10% of normal at all joints. Passive motion at any joint met with a plastic resistance proportional to the stretching force, the resistance being more pronounced in the distal than in the proximal joints. A sudden passive movement resulted in violent clonic contractions of muscle, at first confined to the joint moved, but spreading rapidly to adjacent joints if passive stretch was repeated. Clonic movements were most easily elicited in the hands, feet, and face, in that order, and less easily in the trunk and proximal limb musculature. A light stroking tactile stimulus applied to the face at the corner of the mouth resulted in sustained local spasm, which became clonic if the stimulus was continued. A facile grasp reaction was elicited with a slight moving tactile stimulus of the palm. As the proprioceptive pull on the flexor tendons began, the grasp quickly became clonic and, if traction was continued, spread to the wrist, elbow, and shoulder. Tactile stimulation of the sole led to a tonic foot response; this interfered with interpretation of the plantar response, which was extensor bilaterally. Tactile stimulation of the lips produced sucking movements. Sudden loud sounds or light flashes falling on the retina led to symmetrical clonic flexion movement of both the upper and the lower limbs. If sound or light flashes were repeated, the clonic response was repeated. If sound or light flashes were repeated at a favorable rate, the clonic response became self-sustained and resulted in a generalized seizure. The clonic movements at any joint were of neither uniform rate nor uniform amplitude but diminished in frequency and increased in amplitude as they were repeated; thus, true ankle clonus was not obtained; rather, a response of uniformly diminishing frequency occurred. The finger and other tendon jerks were hyperactive bilaterally. When the patellar tendon was tapped, the response was very marked, with cocontraction of the flexors and extensors of the knee. If the tendon taps were repeated, the response of the quadriceps muscle became repetitive, and almost at once the hip joint, and subsequently all joints, were involved in a self-sustained synchronous myoclonus, culminating in a generalized seizure.

On many occasions during a self-sustained convulsive seizure the patient would indicate by appropriate movement of the head or lips that he had heard and understood a question. While response under such conditions was difficult, simulating unconsciousness, responsiveness was not clearly lost during some closely observed seizures.

A seizure could be easily elicited by passive movement at the elbow. On one occasion there followed symmetrical clonic movements, head retraction, and deviation of the eyes to the left;

clonic movements gradually became slower. There was appropriate response to questions as soon as the last clonic movements ceased.

For a variable period of minutes or hours after a seizure had been stimulated, it was more difficult to elicit a further seizure.

Laboratory Findings.—Examination of the blood, urine, and sputum revealed nothing remarkable. The Kahn reaction of the blood was negative. The cerebrospinal fluid was clear and under an initial pressure of 160 mm. of cerebrospinal fluid and contained 1 lymphocyte per cubic millimeter; the total protein was 24 mg. per 100 ml.; the colloidal gold curve was 0110000000. Roentgenograms of the skull and chest showed no abnormality. Electroencephalograms were abnormal on all occasions and showed generalized synchronous and asynchronous bilateral spike and slow-wave activity (Fig. 2). Visual, acoustic, tactile, and proprioceptive stimuli were effective in producing appropriately localized cerebral electrical responses. A sustained after-discharge resulted from stimulation at a favorable rhythm and duration of stimulus. Detailed studies of the cerebral electrical changes and simultaneously recorded muscle action potentials and mechanical records in relation to stimulus will be reported elsewhere.

Course.—The patient continued to be incontinent, subject to hourly seizures, and helpless because of his rigid quadriplegia and pseudobulbar paralysis. He died Dec. 10, 1949, during a prolonged seizure. Postmortem examination was not permitted.

Case 3 (Family II).—A. P., an Italian boy aged 13, was admitted to the neurological unit of the Boston City Hospital on April 26, 1951, because of convulsive seizures of three years' duration, inability to walk and impaired speech of 10 months' duration, and inability to speak of six weeks' duration.

History.—There were three other siblings. One brother, aged 16 (Case 6), had a distinctly abnormal electroencephalogram but was well; a sister aged 11 years (Case 5) had rheumatic fever; a sister aged 6 years (Case 4) had episodes of "eye blinking, staring, and unresponsiveness." The electroencephalograms in Cases 4 and 5 were definitely abnormal; that in Case 6 was questionably abnormal. The father, an Italian, aged 35, had had seizures from the age of 6 months to that of 1½ years. The maternal grandmother, aged 67, had had a "nervous breakdown" 18 years ago. The maternal great-grandparents died at an advanced age and were unaffected by nervous or mental disease. The birth of A. P. was normal, but he did not sit up until the age of 8 months and did not walk or use two words until the age of 18 months. Scholastic progress was satisfactory until the age of 9 years, when he repeated the fourth grade twice. At the age of 10 years, in July, 1949, he was admitted to the Children's Hospital, Boston, because of vomiting, headache, elevation of temperature, and a speech disturbance, followed by rigidity of the neck and back. Examination of the cerebrospinal fluid revealed 93 white cells per cubic millimeter, 65% of which were polymorphonuclear forms; the total protein was elevated to 40.5 mg. per 100 ml. The course was one of recovery from all symptoms save residual "singsong" speech and a tendency to fall. One month later the patient experienced "weakness of the legs," followed by a generalized seizure. There were episodes of sudden synchronous flexion of both arms. Seizures occurred twice daily thereafter, despite anticonvulsant medication, except for a free interval of two months, after which five seizures occurred over a two-month period, beginning in November, 1949. These were often initiated by a "dizzy spell," with an ensuing fall forward, followed by a generalized seizure; consciousness was lost for half an hour. An ataxic disturbance in gait and dysarthria became apparent in January, 1950, seven months after the onset of seizures, and both increased in severity through the next five months to a point at which the patient was unable to sit without support or to feed himself. Because of inability to sit, walk, talk, or feed himself, and because of status epilepticus, the patient was admitted to the Children's Hospital, Boston, in May, 1950. Significant findings included pronounced nystagmus at a position of rest and marked dysarthria, impaired coordination, and myoclonus.

Seizures thereafter continued to occur about twice a day. For the next 10 months he was unable to move about or sit alone because of progressive weakness; this necessitated removal to bed in January, 1951. In February, 1951, speech became more "jerky"; swallowing was difficult; regurgitation through the nose was frequent, and in early March he stopped speaking but responded by appropriate head movements. Two weeks before admission he became totally unresponsive. Chronic loss of weight and dehydration necessitated readmission to the Children's Hospital, where he received intravenous administration of fluids and nourishment. Two days later

he was "alert," taking fluids and food adequately by mouth. Large amounts of diphenylhydantoin (Dilantin), methylphenylethyl hydantoin (Mesantoin), and phenobarbital were given in the year prior to admission, during which only one seizure occurred. With reduced medication, seizures occurred once a day, but the patient's responsiveness greatly improved, temporarily. Renewed generalized seizures and prolonged unresponsiveness led to his present hospital admission.

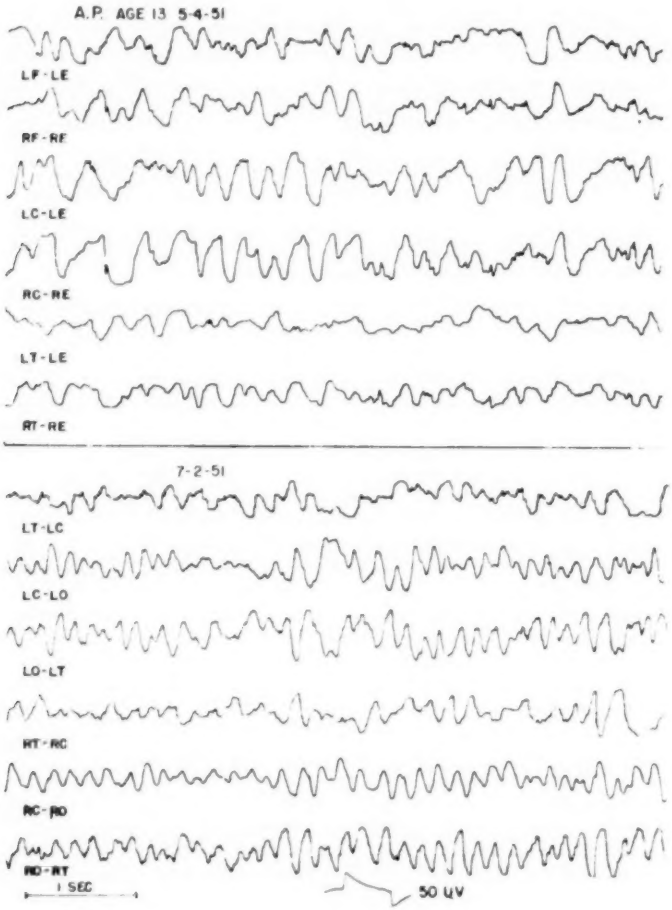

Fig. 3 (Case 3).—Samples of the cerebral electrical activity on two occasions at an interval of one month, during which there was clinical improvement.

Examination.—General medical examination revealed nothing remarkable except for a decubitus ulcer. The patient was without spontaneous speech but was attentive and indicated that he heard and understood spoken commands. He was oriented for place and person, but not for time, and could perform elementary computation but not "serial sevens." During testing he laughed and wept inappropriately and uncontrollably. He could distinguish colors and the face of the examiner. Visual fields were full. The fundi were normal in appearance. The pupils were dilated and slightly unequal but reacted well to light. There was an oscillating nystagmus on lateral gaze. The voice was high-pitched, poorly modulated, and dysarthric. The gag reflex was normal, and he could swallow liquids. The neck was slightly retracted, with a tremor and

rigidity of movement anteroposteriorly. All muscles were diminished in size. He lay with both legs flexed at the hip and knee and extended at the ankle; both arms were flexed at all joints and adducted at the shoulders (Fig. 8, lower part). Motor power was diminished symmetrically at all joints to about 30% except that extension of the left knee was weaker than that of the right. He was unable to sit alone but could stand unsteadily on his toes when supported. There was marked impairment in performance of the finger-to-nose test and the "heel-to-knee-to-toe" test, with rhythmic tremor, bilaterally. There was "plastic" rigidity of the proximal joints. Twitching of the facial muscles occurred, as did sucking movements of the lips. The grasp reflex was elicited easily from both hands. The jaw and deep reflexes were brisk; the knee and ankle jerks were more active on the right than on the left. Abdominal reflexes were absent on the left and diminished on the right. The plantar responses were extensor bilaterally. No defects of sensation were found.

Laboratory Findings.—Examinations of blood and urine revealed nothing remarkable. The Hinton reaction of the blood was negative. The cerebrospinal fluid was clear and under an initial pressure of 100 mm. of cerebrospinal fluid. It contained 2 white blood cells and 4,120

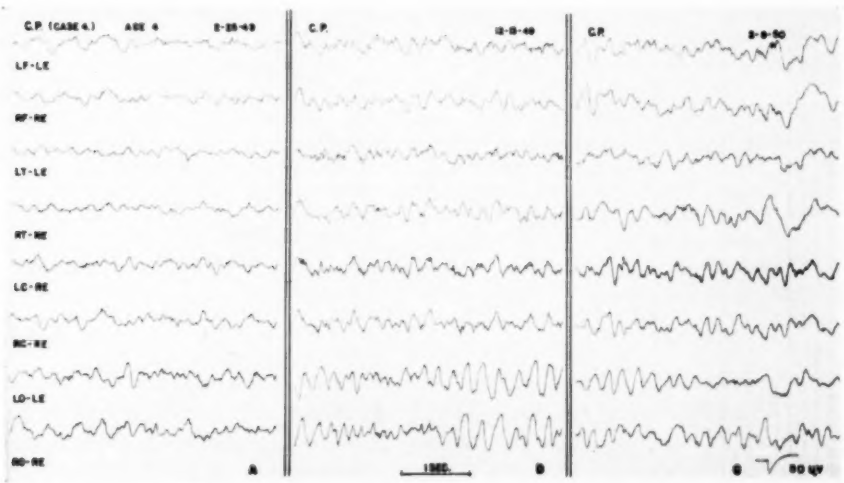

Fig. 4 (Case 4).—Cerebral electrical activity on three occasions, the last (Panel C) one month prior to the onset of seizures. The eyes were open in each instance. For description, see text. (The electroencephalographic records in Cases 4, 5, and 6 were used with the permission of Dr. Randolph Byers, of the Children's Hospital, Boston.)

erythrocytes per cubic millimeter; the Pandy reaction was negative for globulin; total protein measured 42 mg., sugar 70 mg., and chlorides 742 mg., per 100 ml.; the Hinton reaction was negative; the colloidal gold curve was 1222333322. Roentgenograms of the skull and spine showed no abnormality. Electroencephalograms showed abnormal generalized nonsynchronous high-voltage fast-spike and slow-wave forms and a dominant, generally monorhythmic (theta) activity of about 6 cps frequency (Fig. 3).

Course.—During light sleep a seizure occurred in which twitching of the left side of the face was followed by clonic movements of the left hand and forearm and deviation of the head to the left. A few moments later the right side of the face and the right arm and leg, in that order, were affected, followed by loss of consciousness. Myoclonic twitching of the upper limbs and the face independently occurred frequently during sleep in interseizure periods. There were irregular, recurring, sudden synchronous symmetrical contractions of both upper limbs. The course was that of general and striking improvement, punctuated by seizures which were partially controlled by anticonvulsant medication but were easily precipitated by sensory stimulation, such as passive movement. Within the first week the myoclonus ceased. On one occasion

a seizure occurred after intermittent retinal illumination with a flashlight, but, despite many attempts, seizures were not produced by sound, traction on the limbs, or elicitation of the grasp reflex or tendon reflexes. At this time, however, the spontaneous myoclonus had ceased. Gradually, in the following weeks of hospitalization he became fully oriented, and there was such improvement in speech that he could manage conversation and song, even if imperfectly, because of dysarthria. He became able to walk alone, but with a spastic gait. Plastic rigidity of the proximal joints diminished, but generalized weakness persisted, as did extensor plantar responses. The electroencephalogram remained diffusely abnormal (Fig. 3, lower tracings).

After discharge from the hospital he was confined to his wheel chair and was unable to dress himself. He did feed himself. There had been no further seizures.

Case 4 (C. P., a female sibling of A. P. [Case 3]).—Three electroencephalograms, taken at intervals of several months (Fig. 4), showed progressive changes in cerebral electrical activity. The first (Fig. 4 *A*), taken at the age of 4 years, showed scattered random slow activity (1 to 3 cps) somewhat in excess of that expected in a child of this age. The record of Dec. 13, 1949 (Fig. 4 *B*) showed an increase in the amount and relative amplitude of slow activity. The progressive increase in slow activity was further confirmed by the record of Feb. 8, 1950 (Fig. 4 *C*). One month later the patient had the first of several observed seizures. She would "blink, roll her eyes back, twitch, and roll her head back." Seizures were of 10 seconds' duration and occurred several times a day.

Case 5 (D. P., a female sibling of A. P. [Case 3]).—This child had no known seizures. Two electroencephalographic records were obtained at an interval of about two years. The first was normal save for rare bursts of 6 cps activity, of brief duration, in all portions of the recording area except the temporal region (Fig. 5 *A*). A lateralized "sharp spike" discharge occurred on several occasions (Fig. 5 *B*). A record obtained two years later (Fig. 5 *C*) was diffusely abnormal, with bilateral widespread, constant slow activity (about 4 cps), of excessive relative amplitude with considerable "base-line sway."

Case 6 (R. P., a male sibling of A. P. [Case 3]).—This child had no known seizures. The electroencephalogram was normal save for lateralized multiple "sharp wave" discharges (Fig. 5 *D*).

COMMENT

The three patients we have described presented striking similarities in the general pattern of their affliction. Whether or not the pathological process in the second family can be ultimately identified, we wish to emphasize the peculiar significance of epilepsy in this setting and its relation to the larger problem of the nature and significance of "cryptogenic epilepsy."

There was a conspicuous variability of seizure "form" from one member to another and even in the same patient, even though all three patients experienced generalized seizures at one time or another. This variability could at times be related to differences in the stimulus which provoked the myoclonus. It is assumed that "spontaneous" variation was likewise related to variations in the trigger stimulus.

This variability in seizure form is to be expected when the pathological process is that of chronic diffuse neuronal disease. A wide region of central nervous system is in unstable physiological condition, and the individual seizure depends for its form upon the prevailing stimulus pattern, rather than on the intensity of the pathological change in any one locus.

Sjögren [31] found no instances of hereditary transmission of juvenile amaurotic familial idiocy. The disease is familial rather than hereditary. The disease in Family I corresponds to this strict familial pattern. In contrast, Family II has members in two succeeding generations with seizures, establishing its hereditary,

as well as familial, characteristics. Grinker and associates [15a] described a family with myoclonus epilepsy in which both the patient and an aunt exhibited deterioration with myoclonus.

The pattern of clinical disorder and its mode of development strongly suggest that chronic diffuse neuronal disease exists in Family II. The presence of self-limiting seizures of childhood in the parents therefore suggests the possibility of more benign arrested forms of neuronal inclusion disease (lipidosis [?]), which may be transmitted from one generation to another with variable potentiality for manifest disease.

The habitual posture, facies, and speech of the severely affected members of both families were essentially the same. Each of them showed a facies characteristic of pseudobulbar paralysis, with marked dysarthria, progressing to aphonia, and a rigid posture, while standing, of flexion at the neck, trunk, hip, and knees.

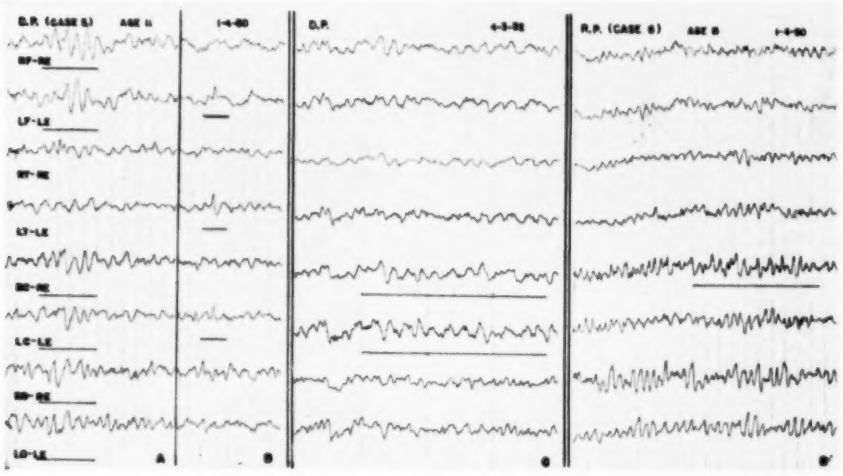

Fig. 5.—Cerebral electrical activity in Cases 5 (D. P.) and 6 (R. P.). See text.

The arms were in adduction and flexion, with flexion of the fingers and extension of the wrists. When the patient was in bed, the flexed posture was accentuated, and plantar flexion at the ankles became evident. Sjögren [31] described the same posture, facies, and speech as characteristic of the late stages of juvenile amaurotic familial idiocy. These gross defects of speech and posture are the usual issue of myoclonus epilepsy and juvenile amaurotic familial idiocy and stand in marked contrast to the benign course of simple cryptogenic epilepsy.

The early abnormal electroencephalographic changes seen in patients with myoclonus epilepsy and their siblings may take a variety of forms, e. g., rare, brief symmetrical paroxysmal bursts of slow activity of good regularity (Fig. 5 *A*); lateralized (Fig. 5 *D*) or localized (Fig. 5 *B*) spikes, or widespread continuous regular slow activity (Fig. 4 *B*), the last form simulating the slow activity characteristic of the normal electroencephalogram of the young. In the four patients with

15a. Grinker, R. R.; Serota, H., and Stein, S. I.: Myoclonic Epilepsy, Arch. Neurol. & Psychiat. **40**:968-980, 1938.

overt seizures, very slow activity of variable frequency characterized the records at the time of the development of seizures (Figs. 3 and 4 *C*).

It is generally recognized that a small number of patients with simple epilepsy show severe progressive deterioration. Hodskins and Yakovlev[15b] described the course and pattern of this deterioration, which results in a posture, gait, and terminal quadriplegia in flexion very similar to those in our own cases and those of Sjögren.

It is of interest that in the few cases of simple epilepsy with progressive deterioration in which pathological reports are available diffuse lesions were described. A 13-year-old boy, examined by Hodskins and Yakovlev,[15b] showed

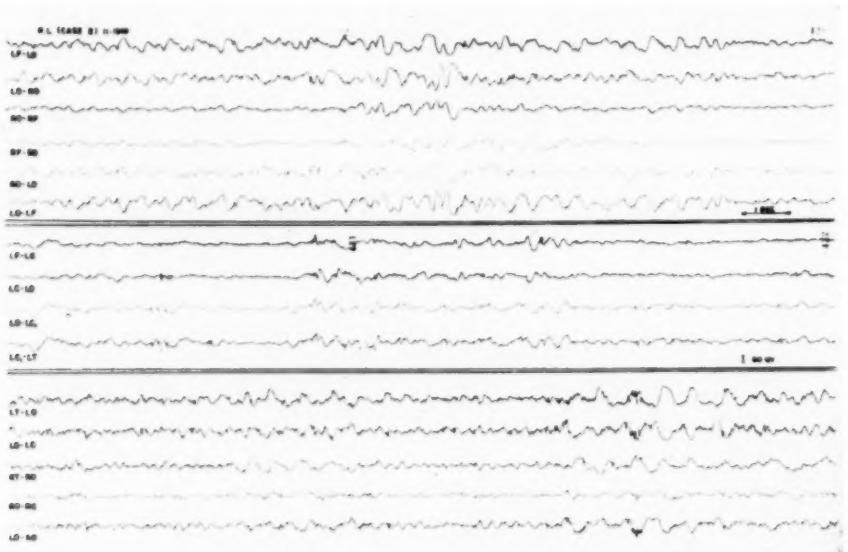

Fig. 6 (Case 2).—Electroencephalogram illustrating periodic bursts of slow waves with intervening quiescence. See text.

"diffuse gliosis and many degenerative and atrophic changes especially in the third and fifth layers of the cortex" and diffuse lesions with glial reaction in the basal ganglia and midbrain. In the third and fifth layers of the cortex there were many nerve cells containing material which stained bright red with scarlet red. Large, swollen cells with eccentric nuclei and pale cytoplasm were seen.

The same authors[15b] examined an epileptic man aged 65 who had experienced his first seizure at the age of 51 and underwent severe "neurosomatic deterioration" one year prior to death. There had occurred diffusely distributed nerve cell loss in the cortex with intracellular inclusion material. The third layer was particularly affected. Swollen and shrunken nerve cells with cell loss and gliosis also occurred diffusely throughout the basal ganglia, hypothalamus, and lower portion of the brain stem. There was prominent atherosclerotic change of cerebral vessels.

15b. Hodskins, M. B., and Yakovlev, P. I.: Neurosomatic Deterioration in Epilepsy, Arch. Neurol. & Psychiat. **23**:986-1031, 1930; Neurosomatic Deterioration in Epilepsy: A Clinicopathologic Contribution to the Concept, with a Report of Two Cases, ibid. **27**:113-137, 1932.

Courtois[15c] described briefly the findings in a case of chronic epilepsy with deterioration as those of "diffuse cortical sclerosis and lesions of an inflammatory nature in the region of the basal ganglia and medulla."

Urechia and Mihalescu[15d] described a 43-year-old patient with chronic epilepsy in whom a "Parkinsonism" syndrome developed; in the brain were found diffuse

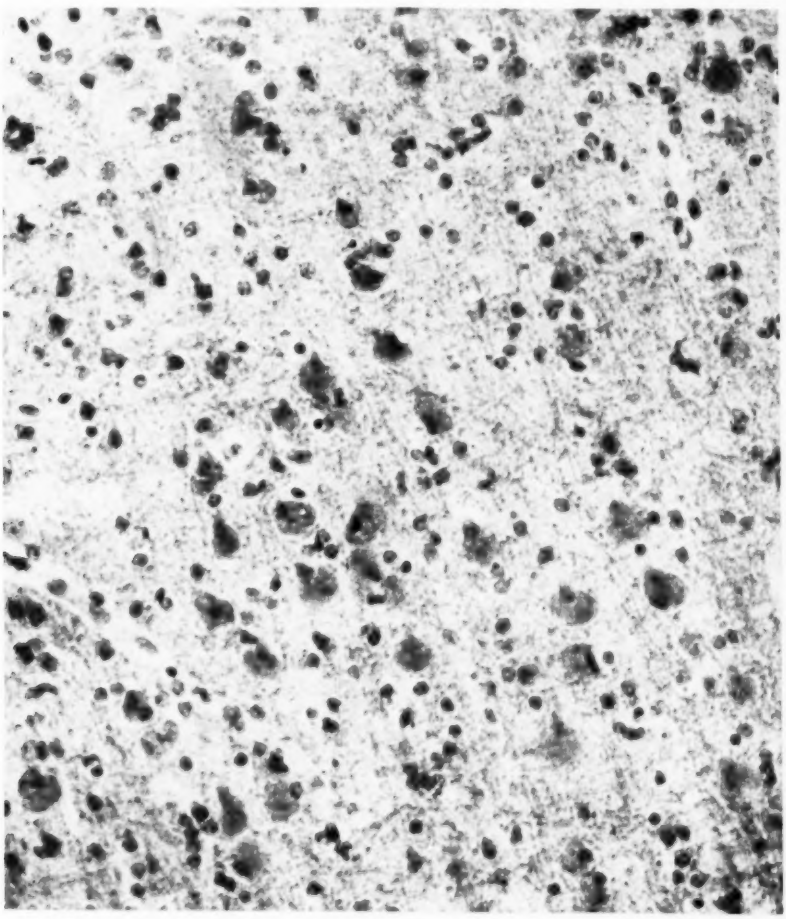

Fig. 7. (Case 1).—Photomicrograph of the third layer of the cerebral cortex. The frozen section, stained with oil red O and counterstained with hematoxylin, shows lipid-filled nerve cells. The changes, typical of "cerebromacular degeneration," are described in the text.

cell loss, chromatolytic changes, and gliosis in the basal ganglia, substantia nigra, and other basal nuclei. Slight, but unspecified, changes occurred in the cortex.

15c. Courtois, A.: Syndrome comitio-parkinsonien: Etude anatomo-clinique, Thesis, Paris, 1928; cited by Hodskins and Yakovlev.[15b]

15d. Urechia, C. I., and Mihalescu, S.: Epilepsie et parkinsonisme: Examen anatomique, Rev. neurol. **2**:99-101, 1927.

That neuronal lipidosis may first manifest itself in middle life is shown by the case of Kufs,[16] in which onset was at the age of 42 and death at the age of 59. Diffuse neuronal lipidosis was demonstrated histologically.

Christensen and Krabbe,[17] Morse,[18] and Ford and associates[19] have recently called attention to a group of cases occurring among infants and young children representing a disorder the final anatomical manifestation of which is diffuse damage and destruction of nerve cells. Changes in the white matter are secondary

Fig. 8.—Photographs taken from motion picture frames illustrating the patient's habitual posture. Above: Case 2; below: Case 3.

16. Kufs, H.: Über einen Fall von spätester Form der amaurotischen Idiotie, Ztschr. Neurol. u. Psychiat. **137**:432-448, 1931.

17. Christensen, E., and Krabbe, K.: Poliodystrophia Cerebri Progressiva (Infantilis): Report of a Case, Arch. Neurol. & Psychiat. **61**:28-43, 1949.

18. Morse, W. I.: Hereditary Myoclonus Epilepsy: Two Cases with Pathological Findings, Bull. Johns Hopkins Hosp. **84**:116-133, 1949.

19. Ford, F. R.; Livingston, S., and Pryles, C. V.: Familial Degeneration of the Cerebral Gray Matter in Childhood, J. Pediat. **39**:33-43, 1951.

to the degeneration of the gray matter; this degeneration may involve gray matter diffusely or may be relatively confined to the cerebral and cerebellar cortex.[20] Freedom,[21] in 1931, reported the clinical and pathological findings in the case of a girl aged 19 who had been retarded in development from birth. She was demented and had exhibited myoclonus and seizures since the age of 5 years. Plantar responses were extensor bilaterally. She walked with legs semiflexed at the knees. The terminal posture was one of flexion contractures of all extremities. There was pronounced diffuse nerve cell loss with gliosis in the cortex, striatum, pallidum, thalamus, hypothalamus, and dentate nuclei. In none of these cases, save one, was there any apparent relation to neuronal lipidosis; Alpers [22] illustrates and comments upon the presence of large amounts of intracellular and extracellular fat in the nerve cells of the basal ganglia in his case. The disorder is characterized by a progressive course, beginning very early in the life of the child. Descriptions of seizures, myoclonus, "hyperkinesis," ataxia, dementia, paralysis, and spastic flexion contractures figure prominently in the protocols. There is no evidence of anoxia, birth injury, intoxication, or inflammation. The disease may occur as a familial disorder.[23] We would emphasize the uniform finding of myoclonus, nearly always in association with epilepsy, in these patients with diffuse degeneration of the cerebral gray matter.

Alajouanine and van Bogaert [24] have reported on two patients aged 61 and 62, respectively, with a progressive cerebral disease which terminated in four weeks with hyperthermia in one patient, and in four months with cachexia in the other. In each there was sustained spasticity of all extremities and of the trunk, neck, and face. In each there were paroxysms of generalized synchronous myoclonus, which were precipitated by slight movement, tendon taps, sound, or flashes of light. Systematic pathological examination revealed only a relatively diffuse glial proliferation with variable scattered nerve cell loss. There was no significant demyelination. The authors believe that the lesions are quite distinct from those of subacute sclerosing leucoencephalopathy. Here, too, the symptomatology is that of diffuse nerve cell disease.

The recent descriptions of "subacute inclusion encephalitis" by Dawson [30]; Brain, Greenfield, and Russell,[25] and Martin, Macken, and Hess [26] have drawn attention to a type of diffuse cerebral degeneration in children, ending fatally in periods varying from nine weeks to two years, associated with myoclonus, epilepsy, and rapidly progressive type of neuronal disease, in which intracellular inclusions are associated with myoclonus epilepsy. In supposed and proved cases of subacute

20. Christensen and Krabbe.[17] Ford, Livingston, and Pryles.[19]

21. Freedom, L.: Cerebral Birth Palsies: A Contribution to Their Pathology with a Report of a Hitherto Undescribed Form, Arch. Neurol. & Psychiat. **26**:524-548, 1931.

22. Alpers, B. J.: Diffuse Progressive Degeneration of the Gray Matter of the Cerebrum, Arch. Neurol. & Psychiat. **25**:469-505, 1931.

23. Morse.[18] Ford and associates.[19]

24. Alajouanine, T., and van Bogaert, L.: Sur une affection caractérisée par une contracture tétanoïde diffuse avec hypercinésies variables et à évolution subaigue mortelle, Rev. neurol. **82**: 21-33, 1950.

25. Brain, W. R.; Greenfield, J. G., and Russell, D. S.: Subacute Inclusion Encephalitis (Dawson Type), Brain **71**:365-385, 1948.

26. Martin, F.; Macken, J., and Hess, R.: Sur une encéphalite subaigue, ayant les caractères de la leuco-encéphalite sclérosante, avec inclusions, Schweiz. Arch. Neurol. u. Psychiat. **66**:217-260, 1950.

inclusion encephalitis of this type, Cobb and Hill [27] described electroencephalographic disturbances characterized at one time or another for a particular patient by a paroxysmal complex of high-voltage slow waves showing a tendency to periodicity as the disease progressed. In the early stages of the disease diphasic or polyphasic spikes were seen in the frontal regions. Radermecker [28] illustrated a similar electroencephalographic disturbance in a case of "subacute sclerosing leucoencephalopathy." Cobb and Hill [27] regarded their electroencephalographic findings as "specific" for the condition of subacute inclusion body encephalitis.

In cases of the progressive "subacute sclerosing leucoencephalopathy" of van Bogaert,[29] myoclonus, seizures, and sensitivity to stimuli of various types are frequently encountered.[30] In this condition there occur electroencephalographic changes which are essentially the same as those described for subacute inclusion body encephalitis. Gray, as well as white, matter is diffusely involved in this disorder, and inclusion bodies of the type described by Dawson for subacute inclusion body encephalitis have been found in some of the cases.[30c]

Cobb, Martin, and Pampiglione [31] have described a common electroencephalographic disturbance which occurred in 12 patients under 9 years of age with cerebral lipidosis, the presence of which these authors believe make the diagnosis of cerebral lipidosis very probable. Two adult deteriorated epileptic patients with lipidosis did not show these electroencephalographic changes. Most characteristic are high-voltage triphasic waves without constant focus, but oftenest widespread and bilaterally synchronous. Such an electroencephalographic disturbance corresponds very closely to that occurring in our Case 2 (Fig. 2).

Thus, several distinct propositions have been put forward in relation to the question of diffuse intracellular nervous disease: First, there are specific electroencephalographic changes for one or another type of pathology, *inter alia*, lipidosis, acute inclusion body encephalitis, and myoclonus epilepsy. Second, myoclonus epilepsy itself is indicative of a specific pathological process (e. g., juvenile amaurotic familial idiocy). Third, myoclonus as a phenomenon is diagnostic of one or another type of these diseases. Our impression is that in these settings myoclonus and epilepsy are symptomatic and relate only to the presence of a diffuse intracellular process, regardless of its nature.

Without necessarily disputing the highly characteristic appearance of the electroencephalographic changes described by Cobb and Hill [27] as occurring with subacute inclusion body encephalitis, we would point out that in our records, obtained from

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27. Cobb, W., and Hill, D.: Electroencephalogram in Subacute Progressive Encephalitis, Brain **73**:392-404, 1950.

28. Radermecker, J.: Leucoencéphalite subaiguë sclérosante avec lésions des ganglions rachidiens et des nerfs, Rev. neurol. **81**:1009-1017, 1949.

29. van Bogaert, L.: Une leuco-encéphalite sclérosante subaiguë, J. Neurol., Neurosurg. & Psychiat. **8**:101-120, 1945.

30. (*a*) Radermecker, J., and Macken, J.: Aspects électroencéphalographique et cliniques de la leucoencéphalite sclérosante subaiguë, Rev. neurol. **85**:341-370, 1951. (*b*) Martin, Macken, and Hess.[26] (*c*) Macken, J., and Lhermitte, F.: Etude clinique et anatomique de la "leucoencéphalite sclérosante subaiguë": Sa place parmi les encéphalites, Bull. Acad. roy. méd. belgique **15**:205-321, 1950. (*d*) van Bogaert.[29]

31. Cobb, W.; Martin, F., and Pampiglione, G.: Cerebral Lipidosis: An Electroencephalographic Study, Brain **75**:343-357, 1952.

a patient with juvenile amaurotic familial idiocy (cerebral lipidosis), there were, at times, paroxysmal slow-wave complexes, which tended to become periodic (Figs. 2 and 6). There were triphasic and multiphasic transient complexes which were, in form and distribution, very similar to those reported by Cobb and Hill [27] and Radermecker [28] in lipidosis, inclusion body encephalitis, and leucoencephalitis. There were in the records from our case with cerebral lipidosis periods of relative electrical inactivity similar to those described as occurring with subacute encephalitis. In neither disease process is there an exclusive correspondence of periodic electroencephalographic discharge with clinical myoclonic phenomena. Thus, the finding of similar electroencephalographic phenomena in verified cases of cerebral lipidosis and verified cases of subacute inclusion body encephalitis suggests to us that the two disorders are not always separable on the basis of electroencephalographic findings alone. We therefore regard these electroencephalographic changes also as symptomatic of this whole class of disorders. At present, only the course of the illness and the rapidity of degenerative changes give any diagnostic indication of the actual nature of the intracellular disease.

The above considerations lead us to conclude that myoclonus epilepsy is the distinctive feature of a series of types of degenerative encephalopathies, ranging from subacute inclusion body encephalitis through the more chronic juvenile amaurotic familial idiocy and related lipidoses to the mildest of chronic or arrested states appearing at any age. The common feature of all these disorders is diffuse primary degeneration of nerve cells. The development of myoclonus and epilepsy in childhood, in association with a progressive pseudobulbar disorder and quadriplegic rigidity in flexion, and with a familial history, is characteristic of juvenile amaurotic familial idiocy. In such a setting the syndrome is striking and unique. The second family reported here shows, in addition, however, that delayed and arrested forms of such conditions may occur, in which some or all the characteristic features are absent. Yet in these cases, too, the same pattern of disorder implies the presence of diffuse intracellular disease.

We believe it to be an important implication that not only these patients with similar syndromes, but also the small proportion of patients with chronic epilepsy undergoing "neurosomatic deterioration," represent a group of chronic diffuse neuronal cellular diseases. Although various types of cellular inclusions have sometimes been found in cases of myoclonus epilepsy, as in Lafora's cases [30a,b] and in cases reported by Hodskins and Yakovlev,[30c] whenever such syndromes occur, neuronal lipidosis may be suspected.

This, in turn, raises the question whether the common occurrence of myoclonic phenomena in cryptogenic epilepsy also represents the presence of such neuronal disease. One approach to cryptogenic epilepsy postulates a focal lesion of the nervous system in nearly every case.[32] Though this question cannot be settled on present evidence, we suggest the hypothesis that the syndrome of degenerative myoclonus epilepsy, and probably any type of unlocalized myoclonus associated with epilepsy, is evidence of the presence of a class of disorder which in more florid form can be recognized as "diffuse intracellular neuronal disease."

32. Alström, C. H.: A Study of Epilepsy in Its Clinical, Social and Genetic Aspects, Copenhagen, Ejnar Munksgaards Forlag, 1950.

SUMMARY

Two families exhibiting the syndrome of progressive myoclonus epilepsy are described. Two siblings of Family I displayed the typical syndrome of progressive familial myoclonus epilepsy of the type described by Unverricht and Lundborg. An affected member of Family I was found to have diffuse neuronal lipidosis ("cerebromacular degeneration"). Neither of the affected siblings had visual defect or pathological change in the fundus.

Family II differed from Family I in several important respects: Epileptic attacks in the form of self-limiting seizures of childhood occurred in one generation, and partial or arrested forms of the syndrome, in the other. The syndrome followed a more benign and remitting course than that in Family I. The pathological process in the second family was not verified, but a review of the problem of myoclonus epilepsy indicates that it uniformly results from diffuse neuronal disease.

HEREDITARY ATAXIA

Difference Between Progeny of Male and Female Affected Members and a Definition of Certain Signs Useful in Detecting the Disease Prior to Onset of Clinical Symptoms

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THE PREVIOUS reports concerning a large family with hereditary ataxia have dealt in detail with the clinical,[1] pathological,[2] and genetic features.[3] In these studies ages of onset were obtained for 32 of the 45 affected members. The average age at time of onset was 26.5 years; however, the age range of 17 to 35 years (except for one member, between 35 and 40 years of age), was a fortunate aspect, for it enabled us to be reasonably certain that if the disease was to appear it would do so before the age of 35.

Another conclusion which emerged through previous studies was that the disease was caused primarily by a simple dominant gene with complete penetrance. The dominant nature of the ataxia was shown by the appearance of the disease, on the average, in one-half the children in the affected sibships and the failure of the ataxia to appear in any member whose parent was not likewise affected. In the absence of the gene the true progressive degenerative process of the central nervous system did not occur. Latent forms of disease, or formes frustes, did not exist in this family. These principles outlined were peculiar to the ataxia in this family and are not necessarily true of all genealogies showing hereditary ataxia.

Owing to the size of the family, each of these conclusions had a high degree of significance and was fundamental in the interpretation of the material in the present report. In summary, these features were as follows: 1. The ataxia as it appeared in this family has a limited age at onset, rarely appearing after the age of 35. 2. The existence of the disease is determined by a mutant dominant gene

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1. Schut, J. W.: Hereditary Ataxia: Clinical Study Through 6 Generations, Arch. Neurol. & Psychiat. **63**:535-568, 1950.

2. Schut, J. W., and Haymaker, W.: Hereditary Ataxia: Pathologic Study of 5 Cases of Common Ancestry, J. Neuropath. & Clin. Neurol. **1**:183-213, 1951.

3. Schut, J. W.: Hereditary Ataxia: Survey of Certain Clinical, Pathologic and Genetic Features with Linkage Data on 5 Additional Hereditary Factors, Am. J. Human Genet. **3**:93-110, 1951.

and is a progressive degenerative condition of certain areas of the central nervous system. 3. The dominant gene has complete penetrance, and hence latent disease, or forme fruste, (i. e., static, nonprogressive disease) did not occur.

MATERIALS AND METHODS

The particular neurologic signs which indicate the presence of hereditary ataxia were dealt with previously,[1] and areas of the central nervous system affected by the degenerative process were outlined.[2] Besides the routine neurologic examination in current use at the Division of Neurology, University of Minnesota, tests were employed in an effort to examine more carefully an incipient dysfunction in those areas of the central nervous system usually affected by the disease. The plan was to examine all persons who had an affected parent, the specific purpose being to define any sign, or group of signs, which might indicate that ataxia was impending among those in or below the risk zone for the disease (17 to 35 years). It occurred to us, however, that isolated neurologic signs, appearing as distinct from the ataxia, could occur among these members and might erroneously be interpreted as indicating that ataxia was imminent. For that reason, a control group consisting of members having an affected parent but past the risk zone were examined. In a sample of this size, unrelated neurologic abnormalities occurring independent of the ataxia should theoretically appear with the same frequency in this group as in patients within the risk zone. On the other hand, signs which may indicate that ataxia was to develop in the future would appear with greater frequency among persons within the risk zone than in those past the age of 35 years.[4]

When it became obvious that a number of persons who were past the age of 35 (past the risk zone) and who were children of an affected parent manifested certain signs of neurologic disease, the reason for this was investigated. Even on cursory examination of the material it became evident that it was the person whose affected parent was the mother who exhibited the abnormalities, whereas children of affected males in this category had no such signs. For purposes of a close statistical evaluation, the material was divided into six categories (groups), which are defined as follows:

1. Members affected with ataxia and whose fathers were similarly affected. Their mothers were free from the disease. Eight such persons were examined.

2. Members affected with ataxia whose mothers were similarly affected. Their fathers were free of the disease. Fourteen such members were examined.

3. Members born of a marriage between an ataxic father and a normal mother and who were past the age of 35 (risk zone). Their average age was 42.7 years, and seven such members were examined. The principles outlined in the introduction explain why it is extremely unlikely that ataxia will subsequently develop in any of these members.

4. Members born of a marriage between an ataxic mother and a normal father and who had passed the risk zone. Their average age was 39.8 years. Similarly, it is extremely unlikely that ataxia will subsequently develop in any of these members. Eight such members were examined.

5. Members born of a marriage between an ataxic father and a normal mother and who were in the risk zone. Under the established principles relating to the dominant inheritance of the true progressive disease, we predicted the future development of ataxia in 50% of these members. If the ataxia should prove to be determined by a partially sex-linked dominant gene, however, an inheritance which cannot be disproved for this pedigree, the males in this category who had an ataxic grandmother have less chance of having the disease than their sisters. Five members were examined in this group.

6. Members born of a marriage between an ataxic mother and a normal father and who were in the risk zone. Similarly, we can predict a 50% incidence of disease in this category in the

4. By definition, an age difference existed between the two groups. Theoretically, the older group would show more scattered evidence of neurologic deficit; hence from a statistical point of view we were justified in making the comparison, for we were attempting to identify changes in the younger group.

future. According to the hypothesis of partial sex linkage, the distribution of the disease between the sexes will also be 1:1 regardless of the sex of the affected grandparent. Twenty such members were examined.

The number of members examined totaled 62. Though the material was very small from a statistical standpoint, it had the advantage of being derived from the same pedigree. Hence, biologically it was more homogeneous than if completely unrelated sibships had been collected. All the relevant clinical findings are tabulated in Table 1. The method of designating individuals in this genealogy in both Table 1 and Table 2 is explained in the legend of the accompanying Chart. For the most part, the examinations were conducted in the home, both of us carrying out the tests. Some children presenting positive toe signs were examined in the outpatient department of the University of Minnesota Hospitals, where their neurologic findings were reevaluated by other members of the staff.[5] Several members of the family were reexamined about five months later, as a check on our original observations. No new signs were discovered on this reexamination; however, it was possible to check on each finding listed in Table 1 and to confirm our original impression of definite abnormalities in members of Groups 4, 5, and 6.

Description and Explanation of Signs Employed in Table 1.—All + signs in Table 1 indicate abnormalities. There are 26 entries; many are self-explanatory. Under intelligence (Entry 1), a history of the school record allowed us to classify most members. Psychometric testing of a select number confirmed our impression as to the validity of these records and led us, for the purpose of Table 1, to divide the members into two groups: (*a*) those of average or above average intelligence and (*b*) those of below average intelligence. The latter group received a + in this Table.

Body Development (Entry 2): Examination of full-view photographs of all members, both from the front and in profile, aided us in making an accurate assessment of body build and development. On this basis, we defined three types: good, fair, and poor. Members of the last type received a + in Table 1, as did any member exhibiting noticeable asymmetry of body development.

Scoliosis or Kyphosis (Entry 3): Any degree of this deformity which could be detected on external examination was interpreted as abnormal. Kyphosis seen on examination and in the profile photographs was not of an extreme degree to receive a + designation.

Other Signs: An abnormal high arch (Entry 4) was photographed and reanalyzed after initial examination. The pupils (Entry 8) were classified as small, medium-sized, and large, and the last type was considered abnormal. The time required to open and close the eyes was constant from time to time in the same person, and when more than six seconds was required to blink 15 times, blinking was interpreted as abnormal. The orbicularis oculi muscle (Entry 10) was prominently affected in all ataxic persons displaying evidence of atrophy of facial muscles. A special attempt was made, therefore, to grade the weakness of this muscle in all groups, and any degree of weakness was interpreted as abnormal.

Jaw Jerk (Entry 16): We have found this reflex to be absent in a relaxed, normal subject. The presence of a definite response is interpreted by many as pathologic, although this is a subject for difference of opinion. In the present series, an obvious response was interpreted as abnormal, even though the reflex was graded like other reflexes.

Deep Reflexes (Entries 20 to 23): Four grades of deep-reflex activity were defined, ranging from complete absence of response to the clonic type. The + sign indicated a normal reflex; ++, a reflex which was very easy to elicit by a slight tap, +++, a response characterized by spread of the reflexogenous areas and one obtained by snapping the fingers on the tensed tendon, and ++++, a clonic response. The +++ and +++ + responses were the only reflexes which were interpreted as abnormal in this study.[6]

5. Dr. A. B. Baker examined a selected few in Group 6.

6. An exaggerated degree of reflex activity, in the absence of additional evidence, such as clonus or extensor toe signs is seldom interpreted as indicating a lesion of the pyramidal system. However, in this study, in which an isolated group was studied, it was of value comparatively and signified merely that those with hyperactive reflexes had greater impairment of their pyramidal system than those with normal reflexes.

TABLE 1.—*Clinical Findings in Members in or past the Risk Period Who Were Born of a Parent Affected with Hereditary Ataxia*

	Intelligence	Body Development	Scoliosis or Kyphosis	Arches of Feet	Anisocoria	Irregular Pupils	Extraocular Muscle Weakness	Pupillary Size	Sluggish Blinking	Orbicularis Oculi Weakness	Finger-to-Nose Ataxia	Adiadokokinesis	Rebound Phenomena	Tandem Stand, Eyes Closed	Gait	Jaw Jerk (Active)	Babinski Hattel Sign	Hoffmann Hand Sign	Biceps Reflex (++++)	Triceps	Knee Jerk	Ankle Jerk	Babinski Toe Sign	Opperheim	Gordon	Oppenheim-Gordon
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
Group III																										
IV-8	—	—	—	+	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
IV-11	—	—	—	—	—	+	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
IV-12	—	—	—	+	—	—	—	—	—	—	—	—	—	—	—	+	—	—	—	—	—	—	—	—	—	—
IV-19	—	—	—	+	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
IV-20	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
IV-24	—	—	—	+	—	—	—	—	—	—	—	—	—	—	—	—	—	+	—	—	—	—	—	—	—	—
IV-29	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	+	—	—	—	—	—	—	—	—	—	—
Group IV																										
IV-17	—	—	—	—	—	—	—	—	+	—	—	—	—	—	—	+	+	+	+	+	+	+	—	—	—	—
IV-18	—	+	+	—	—	+	—	—	+	—	—	—	—	+	—	+	—	+	+	—	+	—	—	—	—	—
IV-31	+	+	—	—	—	+	—	—	—	—	—	—	—	—	—	+	—	—	—	—	+	—	—	—	—	—
IV-34	+	+	—	+	+	+	—	—	+	—	—	—	—	—	—	+	—	+	—	—	+	+	—	—	—	—
IV-42	—	+	—	—	—	—	—	—	—	—	—	—	—	—	—	+	—	—	—	—	+	—	—	—	—	—
IV-47	—	+	—	+	—	—	—	—	+	+	—	—	—	+	—	+	+	+	+	+	+	—	—	—	+	+
V-8	+	+	—	+	—	—	—	—	+	—	—	—	+	+	—	+	—	—	—	—	+	—	—	—	—	—
V-10	+	—	—	+	—	—	—	—	+	—	—	—	+	—	—	+	—	—	—	—	—	—	—	+	—	+
Group V																										
V-30	—	—	—	+	—	—	—	+	—	—	—	—	+	+	—	—	—	—	—	—	—	—	+	+	—	—
V-31	—	—	—	—	—	—	—	+	—	—	+	—	+	+	—	—	—	—	—	—	—	—	—	—	—	—
V-32	—	—	—	—	—	—	—	+	—	—	+	—	+	+	—	—	—	—	—	—	—	—	+	+	—	—
V-54	—	—	—	+	—	—	—	—	—	—	—	—	—	+	—	—	—	—	—	—	—	—	—	—	—	—
IV-22	—	—	—	—	+	—	—	—	—	—	+	—	—	+	—	—	—	—	—	—	—	—	—	+	+	+
Group VI																										
V-12	+	+	—	+	—	+	—	—	—	—	—	+	—	+	—	+	—	—	—	—	—	—	—	+	—	+
V-13	—	—	—	+	—	+	—	—	—	—	—	—	+	—	—	+	—	—	—	—	—	—	—	+	—	—
V-14	—	—	—	—	+	—	—	+	—	—	—	—	+	—	—	+	—	—	—	—	—	—	—	+	—	+
V-15	—	—	—	—	—	—	—	—	+	—	—	—	+	—	—	+	—	+	—	—	—	—	—	+	—	+
V-17	—	—	—	+	—	—	—	—	—	—	—	—	—	—	—	+	—	—	—	—	—	—	—	+	—	+
V-19	—	+	—	—	—	+	—	—	—	+	—	—	—	+	—	+	—	—	—	—	—	—	—	—	—	—
V-20	+	+	—	—	—	+	—	—	—	—	—	—	—	+	—	+	—	—	—	—	—	—	—	—	—	—
V-34	—	—	—	—	+	—	—	—	+	—	—	—	—	+	—	+	—	—	—	—	—	—	—	—	—	—
V-35	—	+	—	—	+	—	+	—	+	—	—	—	—	+	—	+	—	—	—	—	+	—	+	+	—	+
V-36	—	—	—	—	—	—	—	—	+	—	+	—	—	+	—	+	—	—	—	—	—	—	+	+	—	+
V-41	—	—	—	—	+	—	—	+	+	+	+	—	+	+	—	+	—	—	—	—	—	—	+	+	—	+
V-43	—	—	—	—	—	—	—	+	+	—	+	—	—	+	—	+	+	—	—	—	+	—	—	—	—	—
V-44	+	+	—	—	—	—	—	+	+	—	+	—	—	+	—	+	+	—	—	—	—	—	—	—	—	—
V-45	—	—	—	+	+	—	—	+	—	—	—	—	+	+	—	+	+	—	—	—	+	—	—	—	—	—
V-46	—	—	—	—	—	—	+	+	—	—	—	—	+	+	—	+	+	—	—	—	+	—	—	—	—	—
V-49	—	—	+	—	+	—	—	+	—	—	+	—	+	+	—	+	—	—	—	—	—	—	—	+	—	—
V-50	—	—	+	—	—	—	—	+	+	—	—	—	—	+	—	+	—	—	—	—	—	—	—	—	—	—
IV-37	—	—	—	—	—	+	—	—	—	—	—	—	—	+	—	+	—	—	—	—	—	—	—	+	—	—
IV-38	—	—	—	+	—	+	—	—	—	—	+	—	—	+	—	+	—	—	—	—	—	—	—	—	—	—
VI-4	—	—	—	+	—	+	+	+	—	—	—	—	+	+	—	—	+	+	—	—	—	—	+	+	—	+

RESULTS

Comparative Analysis of Differences Among Members Born of Ataxic Males or Ataxic Females (Groups 1 and 2).—All members of these two groups had hereditary ataxia. The particular signs and symptoms of these members have been dealt with in an earlier paper by one of us.[1] This type of ataxia is usually a rapidly progressive disease. As far as neurologic signs were concerned, it made little difference whether the affected parent was male or female. However, the two groups could be compared from other standpoints in an attempt to assess the severity of the disease process. The differences existing between the progeny of male and female members as regards age at onset, age at death, and duration of illness are recorded in Table 2. Besides making comparisons as to age at onset and age at death, we attempted to assess the differences in the severity of the disease in the two groups. In this series of ataxic members, the time that disability appeared was not necessarily related to early death, for the onset of disability marked the time that the patient was placed in a protected environment, and so possibly was freer than the others from intercurrent infection, which would hasten his death. Therefore, "disability," which was defined as existent from the age when the ataxic patient was unable to walk unassisted, was probably a more accurate method of determining the severity of the disease than either duration of illness or age of death.

It is perhaps necessary to point out how statistical calculations based on the figures listed in Table 2 might be misleading.

1. Whereas the number of affected males and females did not vary significantly from the expected 1 : 1, only 9 males had children, whereas 19 women had progeny. This made the total number of children of affected females larger, even though there was no difference between the actual number of children per sibship when the two groups were compared. In many sibships there existed a parent-child correlation between the type of ataxia and its severity, regardless of parenthood. This possibly was the reason that the detrimental effect of affected female parenthood was cumulative, especially to be noted in members in whom the disease had descended through successive generations of women, e. g., V-5. Because of the preponderance of children born of female parents, any statistical comparison of the progeny of the sexes must take this phenomenon into consideration.

2. In Generations III and IV the number of males and females was equal; but in Generation II there seemed to be a preponderance of women, and in Generation V, a preponderance of males. The reason for this phenomenon is not known, but since small differences exist between men and women as regards onset and age of death, this disparity must also be accounted for when one makes close comparisons.

3. As discussed in a recent paper [2] the gene determining the ataxia in this family may be a partially sex-linked dominant. This type of inheritance has a tendency to alter the incidence of male and female affected members in sibships in which the father has inherited the disease from his mother. Conclusive evidence for this type of inheritance awaits such time as certain members of Generations IV and V reach the upper limit of the age at onset. However, should this be found to be true, the incidence of affected men among the progeny of any male who inherited his disease from his mother would be decreased.

For the above-mentioned reasons, it will perhaps be unjustifiable to use statistical methods to arrive at an accurate comparison of Groups 1 and 2 concerning age at onset, duration, and degree of disability. A more accurate appraisal can be realized by comparing select sibships among the progeny of males and females in order to secure documentation for our hypothesis that the progeny of males had ataxia in a milder form.

Progeny of Affected Males (Group 1): Accurate details concerning the vital statistics in the first and second generations were not available. However, the age of death was known for the four affected members of Generation II (all of whom had an affected father); it averaged 42.0 ± 6.0, and as such was higher than

TABLE 2.—*Comparison of Onset and Age of Death in Affected Members Having Ataxia*

Genealogy No.	Age at Death, Yr.	Age at Onset, Yr.	Duration, Yr.
Male Parents			
II-1	42	....	....
II-4	40	....	....
II-5	44	....	....
II-6	32	....	....
IV-7	33	21	12
IV-9	47	25	22
IV-10	36	23	13
IV-14	..	34	....
IV-15	..	33	....
IV-21	..	26.5	....
IV-23	..	27	....
IV-26	37	25	12
IV-27	30	20	10
IV-28	..	30	....
IV-30	..	29.5	....
Average	38.0	26.7	13.8
S. D.	± 5.4	± 4.3	± 4.7
Female Parents			
III-1	41.0	26.5	14.5
III-3	42.0	30.5	11.5
III-4	36	32	4.0
III-5	46	37.5	8.5
III-7	36	31	5.0
III-8	34	21.5	12.5
III-9	34	25.5	8.5
III-15	44	....	....
IV-2	35	20	15.0
IV-4	27	20	7.0
IV-6	42	29.5	12.5
IV-16	40	25.5	14.5
IV-32	42	25	17.0
IV-35	..	28.5	....
IV-36	..	32.5	....
IV-43	..	31.5	....
IV-45	35	30	5.0
IV-46	32	31	1.0
IV-48	..	25	....
V-2	31	22	9.0
V-5	25	17	8.0
V-7	..	25	....
V-9	..	25	....
V-11	26	19	7.0
V-16	..	21	....
Average	36.0	26.3	9.4
S. D.	± 6.9	± 6.5	± 4.5

the over-all average for the 21 deceased members (30.8 ± 6.4). The fact that they were all women added to the significance of their longevity, for as a rule the women had a shorter life span than the men (10 men, 39.6 ± 6.5; 17 women, 35.2 ± 5.8). This phenomenon was present even though modern medical methods

may have prolonged the lives of some of the recently deceased members. Also attesting to the fact that the disease was unusually mild in II-1 was her large family and the recent observation that pregnancy and childbirth speed the course of the disease. This information suggests that the reason for the mildness of the disease in these four females is that their ataxia was inherited from their father.

The children of III-3 included five affected members. The two living members (IV-14, IV-15; age of onset, 34 and 33 years) have ataxia in a very mild form. No member of the entire pedigree had ataxia as long as did IV-9 (22 years), and even at his death, at the age of 47, he was still able to walk, shave, and perform light duties. Information concerning IV-7 and IV-10 was incomplete, but their ages at onset and at death were lower than those of their siblings (IV-7: age at onset 21, age at death 32; IV-10: age at onset 23, age at death 36).

The children of III-5 included an affected woman and man. IV-21, aged 36, who had onset at the age of 27, continues to work as a seamstress, after nine years of the disease. IV-23 has not been observed long enough to permit an accurate statement as to the degree of disability he may exhibit, having had ataxia for only two years.

The children of III-8 included four siblings who were affected. The first two members of the sibship (IV-26: age at onset 25, age at death 37; IV-27: age at onset 20, age at death 30) had a moderately severe form of ataxia, which completely disabled IV-26 before her death. Her other two affected siblings, however, had ataxia in a less severe form (IV-28: age at onset 30, living at 39; IV-30: age at onset 29, living at 33). IV-28 can still walk without assistance, but IV-30 has had ataxia for four years, and many are still unaware of her approaching disability. In this particular sibship, as in some others, there appeared to be a correlation between the severity of the disease in the parent and that in the children, for III-8 had an earlier onset than any of his siblings and died at the age of 32.

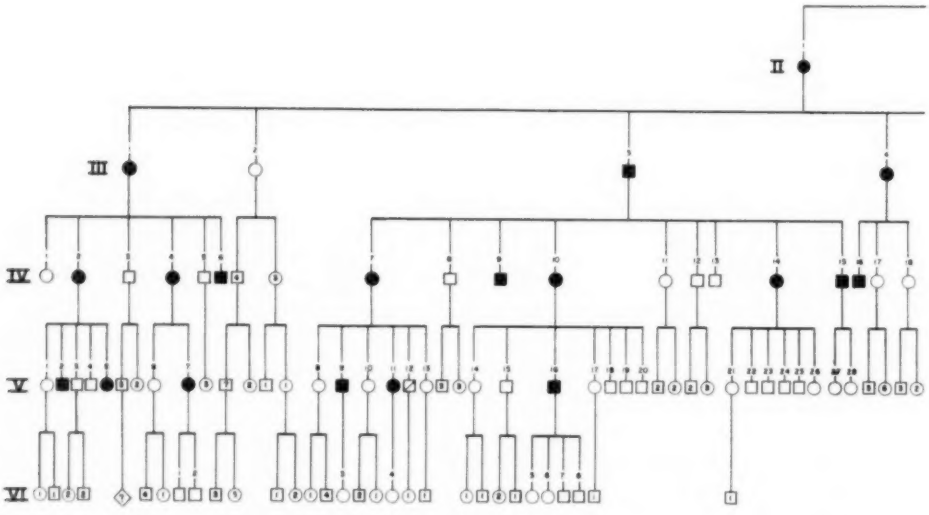
Progeny of Affected Females (Group 2): In Generation III, in which the 10 affected members all had a female parent with the disease, the average age at death for eight deceased members (omitting IV-12 and IV-13) was 39.1 ± 4.7. The age at which three members of Generation V died averaged 27.3 ± 3.2. None of these figures possess statistical significance.

The harmful effect of affected female parenthood on the course of the disease in the progeny is illustrated in the case histories of V-2 and V-5, in which not only the mother, but also the grandmother and great-grandmother, had ataxia. Both these patients, with rapidly progressing ataxia, have died (ages 31 and 25), and the age of onset of V-5 was 17, the youngest for any member of the pedigree. Cases of early death in this pedigree (IV-4, III-4, and IV-46) were notable in that each member had an affected female parent. As a rule, affected members of a given sibship lived longer than their affected parent when the father was ataxic; this was not the case when the mother was the affected parent.

Table 2 shows that there was no difference between the ages at onset in Groups 1 and 2, but the average duration of the disease was 4.4 years less for Group 2. The age at death showed a smaller difference (two years). All these figures are subject to the aforementioned stipulations; nevertheless, they support the contention that the disease process is accelerated if the female is the affected parent.

Comparison of Unaffected Progeny of the Two Sexes Who Have Passed the Risk Zone (Groups 3 and 4).—As noted in the introduction, we have defined the risk zone as covering the age period from 17 to 35 years. After the age of 35 the chance that ataxia will develop in this family is very remote. This means that a member who had passed the risk zone was practically certain to be free of the dominant gene for the disease. The average ages of members of Groups 3 and 4 were 42.7 and 39.8, respectively, and all of them were 35 or past.

As no other neurologic disease was known in this family, we did not expect any of the members to show any special neurologic signs apart from those which might be due to specific environmental conditions.[7] None of them showed signs or symptoms of progressive neurological disease, mentioned as a salient feature of the disease in this series. An occasional sign among these groups could be overlooked, and therefore we considered Group 3 as neurologically normal. As can easily be seen in Table 1, however, this could not be said of Group 4. There was a clear difference between the two groups.



Genealogic chart of a family displaying hereditary ataxia. Arabic numerals above symbols are assigned only within the symbol. A roman numeral denotes the generation, and, when followed by an arabic figure, is the have not reached the age of 35 may yet become ataxic. This chart is based upon all information available in

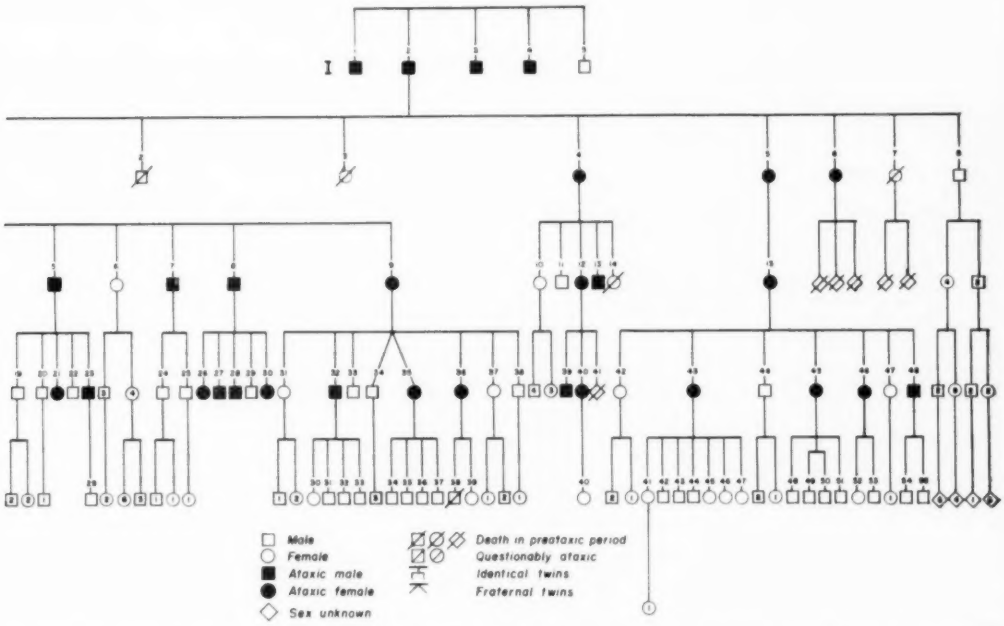
The presence of one or two pathologic signs seldom indicates disease, and therefore we ignored the occasional cases of positive jaw jerk, high arch, a Hoffmann sign, and irregular pupils in Group 3. When we compared Group 3 with Group 4 and took into consideration only those members who displayed at least three different sets of neurologic signs (i. e., signs of damage of different systems), we found a highly significant difference. There could be no doubt that the two groups differed with regard to the neurologic signs listed. It should be

7. An inquiry was made to determine whether any member of these two groups had any other intercurrent disease which could have caused damage to the central nervous system.

also noted that there were more members with lower than average intelligence in Group 4 ($P \pm 0.07$).

We feel justified in stating that members who had passed the risk zone and were born of ataxic mothers showed evidence for symptomless, nonprogressive lesions of the central nervous system, affecting mainly the pyramidal system, while this was not true when the father was the affected parent.

At this point it is necessary to review the reasons that these members might have a "forme fruste" of the disease, i. e., have the "ataxic" gene and, owing to lack of penetrance, display only abortive signs. This idea, however, is not consistent with the genetic analysis already performed in this pedigree,[3] which shows a



to members born of an ataxic parent. Children of nonataxic members are indicated collectively by a number member's genealogic number serving as identfication in the text. Numbered members and their children who January 1952. (See earlier publication,[1] page 6, for pedigree chart as of 1948.)

penetrance of 100%. Furthermore, adding these cases as instances of formes frustes would be inconsistent with any known type of inheritance. The observations made during previous studies has shown that the disease was apparent only in the children of members exhibiting true progressive disease. In other words, the neurologic signs manifested by these members of Group 4 existed without the presence of the gene and hence was not a genetic trait. Therefore, it would be impossible for them to transmit this static abnormality. The hypothesis that these members represent cases of "formes frustes" of the disease does not explain the distribution of the cases, for we would expect them to occur with as great a frequency among the children of affected males as among children of affected

females. Neither were the data consistent with types of any of the well-defined sex-limited, sex-influenced, or sex-linked inheritance or on the basis of selection.

The preceding information has been presented in an effort to show that there are measurable differences between the progeny of male and female ataxic members. These studies failed to uncover the exact mechanism whereby these differences were produced. However, because these differences have been demonstrated, there are some important consequences: First, the neurologic signs prior to the onset of ataxia would have little significance should the child have an affected mother; i. e., they could not be used as premonitory signs of the disease. Second, the existence of this phenomenon apparently has a bearing on the interpretation of the disease process.

Neurologic Signs in Groups 5 and 6.—In these two groups there were members who were still in the risk zone but who did not show signs of progressive disease. It would be important to detect those who are gene carriers, i. e., those in whom ataxia will later develop. Theoretically, 50% of these groups are carriers; in other words, every member has a 50% chance of development of ataxia. Both groups exhibited neurologic signs, as shown in Table 1. The fact that we discovered a phenomenon which increased the measurable neurologic signs in persons born of affected females made the interpretation of Group 6 very difficult. As a consequence, all the signs found in Group 6 could not be relied upon as indicating the presence of the "ataxia" gene, as the mother was the affected parent. Only if additional signs were present could a member of Group 6 be suspected of being a carrier. Thus, in this group, of 20 members, if we are not too rigid in the interpretation of the test "tandem stand with closed eyes," which, as a matter of fact, cannot be performed very well in a random sample, the following nine members did not display this sign: V-13, V-14, V-15, V-17, V-34, V-43, V-49, V-50, and IV-38. We are inclined to consider it less likely that these persons will have hereditary ataxia than will the nine members who were unable to stand tandem with their eyes closed and had, in addition, cerebellar signs and pathologic reflexes.

A congenital weakness of some extraocular muscle, present in V-2 and V-16 prior to onset of their ataxia, was considered a significant premonitory sign. It was present in V-35, V-45, and VI-4 and in two children of IV-14, who were not examined. Large pupils was also interpreted as an important sign, but its presence was usually constant within sibships, e. g., V-30, V-31, and V-32. This method of analysis gives a rough 50:50 division of the group, which corresponds to the theoretical expectation. It is admitted that the procedures by which we identified these members was purely one of trial and error. Only by observation of this group for at least 10 years in order to see in whom ataxia will develop can the value of these interpretations be determined.

In Group 5, in which each member had an affected male parent, signs of pyramidal tract involvement are probably of greater consequence. Therefore, we considered it likely that V-31 and V-54, who had cerebellar signs, were likely to have ataxia.

SUMMARY

Members of a large pedigree showing hereditary ataxia were examined neurologically. The 62 available members having an affected parent were classified as (1) persons who exhibited true progressive hereditary ataxia, (2) those who had

passed the risk zone, or those who had reached the age of 35, without exhibiting signs of progressive neurologic disease, and (3) those who were within the risk zone and who at the time of this report did not show any sign of progressive disease. This risk period was defined as between 17 and 35 years of age. Each of these three categories was divided according to whether the affected parent was a man or a woman, the classification constituting six groups in all.

When the essential differences in the groups were subjected to a statistical analysis, certain significant differences appeared. Affected members who had an affected mother showed evidence of severer disease and a shorter course on the average than did members born of affected male parents. In members past the risk zone in whom we can be reasonably sure that the true progressive disease will not subsequently develop, there appeared evidence of nonprogressing neurologic abnormalities among those having a female affected parent, while this was not true of those having a male parent with the disease.

These measurable neurologic signs among all progeny of female ataxic patients interfered with the detection of signs which may have been useful in identifying members destined to have the disease in the future. It was difficult, therefore, to determine whether this "maternal effect" was producing neurologic signs in this group, or whether we were influenced by the statistical finding that 50% of the patients would subsequently have the disease. Nevertheless, a few signs were selected as premonitory, which may or may not prove useful in predicting impending ataxia; the value of these observations will depend entirely upon whether the disease actually develops in these members whom we chose.

EFFECTS OF CHRONIC BARBITURATE INTOXICATION ON MOTIVATION AND MUSCULAR COORDINATION

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INVESTIGATIONS of chronic barbiturate intoxication have yielded considerable information on physiological functioning,[1] intellectual impairment, and personality changes [2] during the course of addiction. The present study is an attempt to add to this information by delineating several aspects of readiness to respond (motivation) and muscular coordination during the course of chronic intoxication with certain barbiturates and during the periods of withdrawal of drugs and of recovery from the drug effects.

Clinical studies from this laboratory [1] have amply shown that acute or chronic intoxication with large amounts of barbiturates (secobarbital, pentobarbital, amobarbital) produces nystagmus, incoordination, ataxia in gait and station, and coarse tremors of the hands. The muscular incoordination of intoxicated persons is so obvious that the measures obtained in the present study were recorded mainly for purposes of quantification and comparison. However, the effects of changing motivations upon the disorganized behavior observed during intoxication and withdrawal have not been investigated.

Changes in simple reaction times to visual stimuli, when the foreperiod, or delay time between warning and stimulus lights, was varied in randomized order, provided the data on one particular type of motivation. Recently, when considering this reaction, Poulton,[3] Davis,[4] and others have placed emphasis upon the develop-

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The clinical, biochemical, and physiological findings in this study will be reported later by H. F. Fraser, H. Isbell, A. J. Eisenman, and A. Wikler.

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1. Isbell, H.; Altschul, S.; Kornetsky, C. H.; Eisenman, A. J.; Flanary, H. G., and Fraser, H. F.: Chronic Barbiturate Intoxication: An Experimental Study, Arch. Neurol. & Psychiat. **64**:1-28, 1950. Isbell, H., and Fraser, H. F.: Addiction to Analgesics and Barbiturates, J. Pharmacol. & Exper. Therap. **99**:355-397, 1950.

2. Kornetsky, C. H.: Psychological Effects of Chronic Barbiturates Intoxication, A. M. A. Arch. Neurol. & Psychiat. **65**:557-567, 1951. Wikler, A.: Sites and Mechanisms of Action of Morphine and Related Drugs in the Central Nervous System, Pharmacol. Rev. **2**:435-506, 1950; Mechanisms of Action of Drugs That Modify Personality Function, Am. J. Psychiat. **108**:590-599, 1952.

3. Poulton, E. C.: Perceptual Anticipation and Reaction Time, Medical Research Council, Applied Psychology Research Unit, Cambridge, England, 1950.

4. Davis, R. C.: Set and Muscular Tension, Indiana University Publications, Science Series No. 10, Bloomington, Ind., Indiana University Bookstore, 1941.

ment of a "set," or a readiness to respond. The efficiency of the response depends upon the preparatory behavior that occurs immediately prior to an expected stimulus, or immediately subsequent to an unexpected stimulus. Kantor [5] has made wider application of this concept of anticipatory, or precurrent, behavior in defining motivation as readiness to respond. The latter formulation will be used for interpreting some of the findings on former opiate addicts during and after barbiturate intoxication; and the terms "motivation," "set," and "readiness to respond" will be used interchangeably.

It is quite evident, however, that changes in motivation are not responsible for all changes recorded in reaction time. The behavioral history of the organism determines whether it can respond in any circumstances, and the immediate physiological condition determines to what degree it can respond at a particular time. The immediate situation and the condition of the organism determine the manner and time of occurrence of the response. The class and momentary level of motivation may be inferred from consideration of experimental conditions and of pertinent responses.

In the present study, motivational conditions were very similar to those encountered in everyday life. The subjects (former opiate addicts) were merely instructed to react as quickly as possible, and differences in reaction time corresponding to the various foreperiods were evaluated as being due to motivational differences. It was not possible to alter motivation to an extreme degree, as is being done in current studies on the effects of morphine, in which drug rewards are offered that are commensurate with speed [6]; therefore, we could not determine the extent to which impairment in performance could be overcome by introducing very potent incentives.

One interest in the study was simply investigatory, supplementing knowledge already gained, while another interest was very practical. Since it has been reported that measures of both reaction time and muscular coordination rank high as indicators of accident proneness,[7] the second interest was directed toward indicating what might be expected when chronic barbiturate users operate potentially dangerous machines. Thus, simple responses to visual stimuli, using various delay periods (foreperiods) and sustained, coordinated responses were measured during (*a*) intoxication, (*b*) after abrupt withdrawal of drugs, and (*c*) after recovery from drug effects.

SUBJECTS, APPARATUS, AND PROCEDURE

On admission to the hospital at Lexington, 10 male patients who were addicted to barbiturate and narcotic drugs volunteered for the experiment. Narcotic drugs were gradually withdrawn over a period of 10 to 14 days, and addiction to barbiturates was continued by oral administration of secobarbital (Seconal). The drug was given six times a day in oral doses sufficient to maintain intoxication at a degree that usually permitted ambulatory management; the dose was varied for the different subjects in an attempt to maintain them at maximum and com-

5. Kantor, J. R.: Toward a Scientific Analysis of Motivation, Psychol. Rec. **5**:225-275, 1942.

6. Hill, H. E.; Belleville, R. E., and Wikler, A.: Unpublished data.

7. (*a*) Allgair, E.: What the Ford Tests Showed, Public Safety **19**:14-15, 1941. (*b*) Selling, L. S.: The Young Traffic Offender, Am. J. Orthopsychiat. **12**:241-251, 1942. (*c*) Soddy, K.: Psychological Aspects of Accidents and Accident Prevention, Brit. M. J. **2**:623-626, 1947.

parable levels of intoxication. Maximum chronic intoxication was continued from 35 to 90 days, depending upon clinical conditions, and the dose for the last two weeks of chronic intoxication ranged from 0.9 to 2.2 gm. a day.

Each man was tested at the same time each day, usually immediately prior to the 2 p. m. medication. Testing was begun two weeks prior to the withdrawal date and was continued, with daily sessions when possible, (*a*) during the last week of addiction, when stabilization on the drug dosage had been assured, and (*b*) after withdrawal of barbiturates, and was concluded (*c*) after recovery from drug effects had occurred.

Two pieces of apparatus were employed. Simple visual reaction times, using four foreperiods (one, two, four, and eight seconds), presented in randomized order, were recorded by means of a chronoscope and supplementary instruments, which have been described in an earlier paper.[8] Forty responses were taken at each session. The first 20 reactions were separated from the second 20 by administration of 10 trials on a test of muscular coordination.

Apparatus for the test of coordination consisted of a vertical tracing path, which the subject was instructed to negotiate without touching the sides. Two 18 in. brass-edged rulers were secured to a vertical piece of plywood, separated at the lower ends by 1 in. (2.54 cm.) and at the upper ends by 1/16 in. (1.5 mm.). The area of plywood between the rulers was entirely cut away, and the brass edges and metal-tipped stylus were wired to a battery. The subject was seated in front of the board, which was at waist level, and was instructed to raise the stylus slowly as high as possible without touching either side. When contact between stylus and ruler occurred, a neon light flashed, and the experimenter recorded the distance traversed in inches. Each subject was given 10 trials, with no rest periods, accompanied with cautioning to maintain the arm fairly straight, with the thumb on top of the stylus, and not to support the arm by body or knee.

In following the course of changes in readiness to respond and muscular coordination, each man was used as his own control. For each subject, mean measures of reaction time and coordination obtained during addiction and during the 18 days following abrupt withdrawal of the drug were compared with those recorded after recovery (three to five months after abrupt withdrawal of drugs). These several conditions are presented in Tables 1, 2, and 3 and Charts as "Intoxication," "Withdrawal," and "Recovery." The withdrawal condition, indicated in Chart 1 as "Days of Abstinence," was divided into the seven parts shown in Table 1, each part usually covering a two-day phase.

In addition to comparisons of mean reaction times of the various phases, comparisons were made of reaction times recorded for the four different foreperiods within each phase. This was an attempt to evaluate differential sensitivity during each of the conditions. It was found that two-second foreperiods produce shorter mean reaction times than the one-, four-, or eight-second foreperiods. Thus, deviations from this order of efficiency would indicate that changes had occurred in preparatory set, or readiness to respond.

As a check on the reliability of the measures obtained after recovery, reaction times and coordination scores were obtained on a control group of postaddicts who had not received drugs for several months prior to the test.

Statistical significances of differences were obtained by using the difference method.[9] If standard deviations (measures of scatter) are significantly different, or if the distribution of scores is not normal, the use of the *t* test in assaying the difference between means may be open to question. Therefore, in the present study the reliabilities of the *P* values were checked by a nonparametric technique.[10] They were found to be in close agreement.

It should be emphasized that testing was accomplished, often with considerable difficulty, immediately prior to the administration of the 2 p. m. medication, when the patient was functioning at an optimal level. Not infrequently he was transported to the testing room in a wheel

8. Hill, H. E.; Kornetsky, C. H.; Flanary, H. G., and Wikler, A.: Studies on Anxiety Associated with Anticipation of Pain: I. Effects of Morphine, A. M. A. Arch. Neurol. & Psychiat. **67**:612-619, 1952.

9. Edwards, A. L.: Experimental Design in Psychological Research, New York, Rinehart & Company, 1950, p. 276.

10. Mann, H. B., and Whitney, D. R.: On a Test of Whether One Variable Is Stochastically Larger Than the Other, Ann. Math. Statist. **18**:50-60, 1947.

chair and required assistance in seating himself at the apparatus. If testing had been attempted even 30 minutes subsequent to the medication, the patient would have been so poorly oriented and coordinated that measurement of these particular performances would have been impossible.

TABLE 1.—*Comparison of Mean Reaction Times of Recovery with Those of Intoxication and Withdrawal*

Mean Reaction Times						
Intoxication	Withdrawal	Days	Diff.	S.E. Diff.	t	P *
0.491	0.347	1-2	0.144	0.0405	3.56	< 0.01
Intoxication	Recovery					
0.483	0.233	...	0.250	.....	7.31	< 0.001
Recovery †	Withdrawal					
0.243	0.355	1-2	0.112	0.0261	4.27	< 0.01
0.234	0.293	3-4	0.059	0.0248	2.38	> 0.10
0.216	0.275	5-6	0.059	0.0259	2.28	> 0.10
0.235	0.264	7-8	0.029	0.0145	2.00	> 0.10
0.237	0.254	9-10	0.017	0.0061	2.77	< 0.05
0.234	0.230	11-14	0.004	0.0069	0.58	> 0.50
0.226	0.223	15-18	0.003	0.0069	0.44	> 0.60
Control ‡						
0.233	0.235	...	0.002	0.0135	0.15	> 0.90

* The P column indicates the probability of the results occurring by chance in 100 repetitions.
† The differences in mean recovery and withdrawal (Days 1-2) reaction times are due to the inability of some subjects to participate during several of the periods.
‡ The last comparison is between reaction times for recovery and those of a control group of 22 post-addicts.

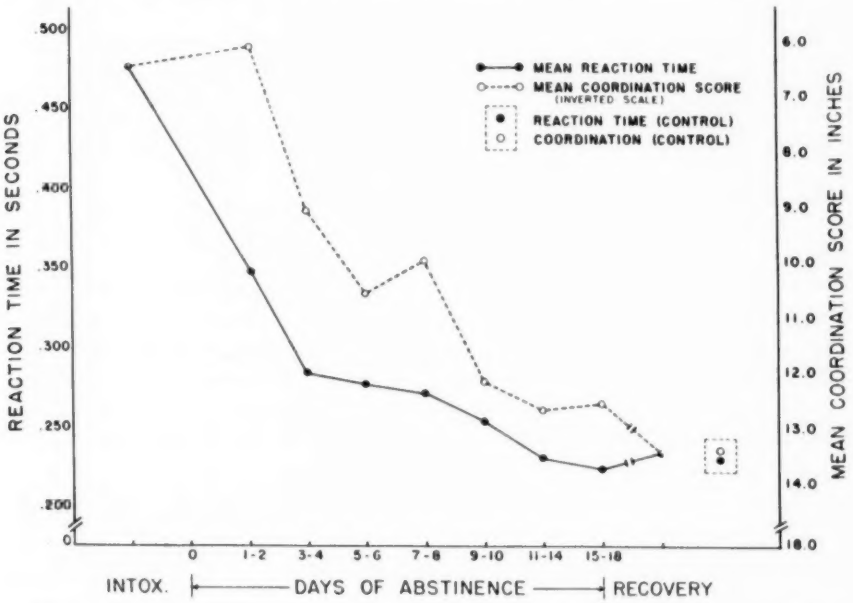

Chart 1.—Mean reaction times and coordination scores for intoxication, withdrawal (abstinence), and recovery, and similar measurements on a control (post addict) group.

RESULTS

A. Mean Reaction Time (arithmetical reaction time means for each condition, irrespective of foreperiod).—Table 1 and Chart 1 present comparisons of mean reaction times of recovery with those for intoxication and withdrawal (abstinence)

and for the control group of postaddicts. Reaction times for intoxication were found to be more than twice as long as those for recovery. Although, in general, improvement was noted from day to day after withdrawal of secobarbital, a very significant trend of impairment continued through the 10th day. After this, no significant differences between the withdrawal and the recovery reaction times were detected. The gradual improvement in reaction time is statistically evaluated in the *P* column in Table 1 and can be directly observed in the "Diff." column. This Table also shows that a very small difference, which could easily have occurred by chance, was found between recovery reaction times and those obtained for the control group of postaddicts.

TABLE 2.—*Comparison of Mean Reaction Time for the Various Conditions According to Delay Between Warning and Stimulus Lights*

Foreperiod, Sec.	Respective Means		Diff.	S.E. Diff.	*t*	*P*
Intoxication (N = 10)						
1 vs 2	0.476	0.469	0.007	0.0117	0.60	>0.50
1 vs 4	0.476	0.469	0.007	0.0253	0.28	>0.70
2 vs 4	0.469	0.469	0.000	0.0154	0.00	>0.90
1 vs 8	0.476	0.489	0.012	0.0218	0.55	>0.50
2 vs 8	0.469	0.489	0.020	0.0141	1.44	>0.10
4 vs 8	0.469	0.489	0.020	0.0182	1.10	>0.20
Withdrawal (N = 8): Days 1-2						
1 vs 2	0.374	0.304	0.070	0.0164	4.27	<0.01
1 vs 4	0.374	0.332	0.042	0.0127	3.31	<0.02
2 vs 4	0.304	0.332	0.028	0.0127	2.20	<0.10
1 vs 8	0.374	0.378	0.004	0.0255	0.16	>0.80
2 vs 8	0.304	0.378	0.074	0.0334	2.16	<0.10
4 vs 8	0.332	0.378	0.046	0.0250	1.84	>0.10
Recovery (N = 9)						
1 vs 2	0.227	0.233	0.004	0.0050	0.68	>0.50
1 vs 4	0.227	0.242	0.015	0.0063	2.38	<0.05
2 vs 4	0.233	0.242	0.009	0.0055	3.45	<0.01
1 vs 8	0.227	0.239	0.012	0.0048	2.50	<0.05
2 vs 8	0.233	0.239	0.006	0.0061	2.62	<0.05
4 vs 8	0.242	0.239	0.003	0.0059	0.51	>0.60

B. Mean Reaction Times According to Foreperiods (effects of varying the delay time between warning and stimulus lights).—Table 2 presents a comparison of mean reaction times for the various foreperiods, which are indicated in seconds in the first column; graphic comparisons are made in Chart 2.

Reaction times obtained three to five months subsequent to withdrawal of the drug appear to be "normal." The order of efficiency of the various delay periods is that expected under control conditions; the two-second delay is most efficient, followed, respectively, by the one-, four-, and eight-second delays. As can be observed in Table 2, varying the foreperiods produced significant changes in reaction time, three of the six comparisons showing less than the 5% level of confidence and one less than the 1% level of confidence when a two-sided distribution of *t* was used.

During the intoxication period no differences of statistical significance were obtained by varying the foreperiod. However, it will be observed in Chart 1 that all reaction times were greatly lengthened and that there was a comparatively slight trend for the short and the long foreperiods to be relatively more difficult.

The first phase of withdrawal was also analyzed in this way. It can be seen that the order of efficiency of the various foreperiods was very different from that

of either intoxication or recovery. There were a general shortening of reaction time (a decrease in mean time from 0.491 second, for intoxication, to 0.347 second) and much more sensitivity to differences in stimulus delay. The two-second foreperiod was optimal, as it was for recovery, followed by the four-, one-, and eight-second delays, in that order. Statistically significant differences were demonstrated. It will be observed in Table 3 and Chart 2 that the standard deviations for intoxication, withdrawal (Days 1-2), and recovery differed widely; the three

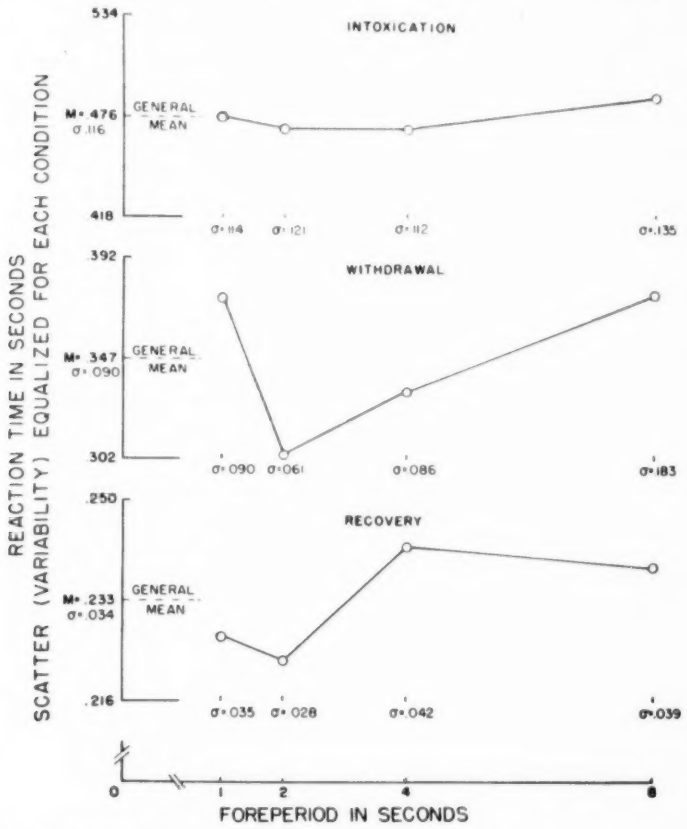

Chart 2.—Differential sensitivity to changes in foreperiod (delay time) as shown by relative efficiency of reaction time. The mean scores have been equalized on the ordinate according to the respective means and standard deviations.

possible comparisons of these standard deviations resulted in statistically significant values of *t*.

C. Coordination.—Table 3 and Chart 1 present data obtained on the test of sustained, coordinated movement. The mean score for intoxication and that for withdrawal (Days 1-2 of abstinence) were practically identical, and each was less than half that for recovery; statistical comparisons showed that impairment was very severe. Although a strong trend of improvement occurred up to 15 to 18

days, when testing was discontinued, impairment was still present that nearly reached the 5% level of confidence. Extreme variability of performance during intoxication and early withdrawal were also shown. Table 3 also presents data showing that coordination measures taken during recovery were only very slightly different from those obtained for the postaddict (control) group.

The rank-order correlation coefficients between reaction time and coordination were as follows: 0.49 during intoxication, 0.43, 0.33, 0.98, 0.00, —0.22, 0.04, and —0.25 for the various phases of withdrawal, and —0.10 for recovery. These coefficients can be accepted only as indications of true relationships, since the number of subjects used was small. However, we can probably accept the trend as being reliable, because the first four correlations are strongly positive. The relationship, then, appears to be positive during intoxication and immediately after withdrawal of drugs and either zero or slightly negative after recovery has occurred.

TABLE 3.—*Comparison of Mean Coordination Scores for Recovery with Those for Intoxication and Withdrawal*

Mean Coordination Scores						
Intoxication	Withdrawal	Days	Diff.	S.E. Diff.	*t*	*P*
6.1	6.1	1-2	0.0	1.52	0.00	>0.99
Intoxication *	Recovery					
5.8	13.9	...	8.1	1.23	6.59	<0.001
Recovery	Withdrawal					
14.1	7.0	1-2	7.1	1.89	3.76	<0.02
13.8	8.4	3-4	5.7	1.32	4.32	<0.02
13.5	10.6	5-6	2.9	0.97	3.00	<0.05
14.0	10.9	7-8	3.1	0.96	3.23	<0.02
13.8	12.2	9-10	1.6	0.67	2.39	>0.05
14.2	12.7	11-14	1.5	0.42	3.57	<0.05
13.7	12.6	15-18	1.1	0.39	2.82	>0.05
	Control					
13.5	13.6	...	0.1	0.62	0.16	>0.90

* The differences in mean recovery and intoxication reaction times are due to the inability of some subjects to participate during several of the periods.

COMMENT

Measures indicative of very significant incoordination were obtained during intoxication and withdrawal. Although the incoordination observed during intoxication and that noted in the first days of withdrawal differ in nature,[11] both represent extreme impairment. Any degree of efficient, sustained muscular control is very difficult to attain either under the influence or shortly after the withdrawal of barbiturates. Recovery occurred at a very uniform rate, but it was not complete 18 days after withdrawal of medication. Recovery of performance on the two tests did not occur at the same rate, probably because coordination requires sustained control. Measures of reaction time returned to control levels much sooner than did measures of coordination; thus, coordination appears to be the more sensitive indicator of physiological impairment.

Recorded coordination measures of intoxication and withdrawal (Days 1-2) did not differ, while measures of reaction time for these two conditions differed very significantly. We may therefore conclude that improvement in reaction time

11. Isbell, H.: Personal communication to the authors.

is not due to a concomitant improvement in coordination. It is also apparent from Table *2* and Chart *2* that sensitivity to differences in the motivation that was used for reaction time in this study returned during the first days of withdrawal, whereas there was no improvement in coordination.

In most circumstances it is difficult to produce an increase in the latency of the simple response of key pressing if the subject is attempting to respond as quickly as possible; thus, the differences between intoxication and recovery reaction times represent tremendous depression of behavior. Regardless of the variables involved, responses dropped to a point of extreme inefficiency. Changing the length of the time to prepare (foreperiods) did not result in significant differences in reaction time during intoxication, as it did for recovery. This lack of sensitivity and relative inability to respond to instructions that are commonly used in experimentation shows extreme inability to change set, and it may be surmised that such impairment would be reflected during intoxication as inability to react effectively in emergencies. However, it should be recognized that motivations of great strength were not used and that their use might have resulted in some decrease in reaction time. This inference is supported by current studies[6]: although reaction times recorded under usual instructions are significantly slowed one hour after injections of 250 mg. of pentobarbital, such impairment disappears when subjects earn drug rewards that are commensurate with quickness.

Rank-order correlation coefficients for intoxication show that there was no relationship between dose level and reaction time for our subjects, and a slight, nonsignificant positive relationship between dose level and coordination score. It was also shown that there are a zero or slightly negative correlation between the two tests under control conditions and a reliable positive relationship during drug conditions. Thus, during intoxication these tests measure some common factors, but during nondrug conditions they do not.[12]

Alertness in anticipating situations which might produce accidents has been stressed as a prerequisite of a safe driver or machine operator. Although very fast reaction time and exceptionally good muscular coordination do not necessarily prevent or eliminate accidents, the reverse has been shown to hold true with considerable predictability; slow reaction time and impaired muscular coordination are associated with proneness to accidents.[7] Also, Selling[7b] and Soddy[7c] have both reported, as would seem logical, that less studied factors, such as momentary impulsivity, indifference to authority, or antagonism to law, are positively related to automobile accidents. In this connection, it has been found that the drug addict frequently presents this type of personality picture.[13]

Reaction time is a measure of a person's ability to prepare for and execute a single quick response, such as that of applying the brake while driving an automobile. Performing a continuous series of adjustive movements, as measured by the test of coordination, appears to be somewhat similar to steering a motor vehicle or operating various industrial machines. Although no statistics are available,

12. A correlation of —0.32 between reaction times recorded in a simulated automobile steering device and measures of steadiness has been reported by Travis (Travis, R. C.: An Experimental Analysis of Dynamic and Static Equilibrium, J. Exper. Psychol. **35**:216-234, 1945).

13. Hill, H. E., and Belleville, R. E.: An Application of the Minnesota Multiphasic Personality Inventory to the Narcotic Drug Addict, to be published.

it would thus appear that barbiturate users may be extremely hazardous machine operators.[14] In addition to having slow reaction times and muscular incoordination, they lack the ability to anticipate and prepare for situations that demand continuous alertness and muscular control.

SUMMARY AND CONCLUSIONS

Ten male patients, addicted to barbiturates upon arrival at the Public Health Service Hospital, Lexington, Ky., who volunteered for the study were maintained on large doses of secobarbital (Seconal) for periods ranging from 35 to 90 days. Reaction times to visual stimuli and quantified measures of muscular coordination were taken (*a*) during the last week of addiction (intoxication), (*b*) after abrupt withdrawal of the drug, and (*c*) after recovery from drug effects.

Great loss of coordination was found during intoxication and during the first eight days of the withdrawal period, with gradual improvement continuing through the remaining 10 days. Reaction time was found to be very greatly impaired during intoxication and early in the withdrawal period; but, unlike coordination, it showed significant improvement soon after withdrawal and thereafter gradually returned to the control level.

Differences in reaction time corresponding to various foreperiods, or delay times, were evaluated as motivational differences; i. e., they were evaluated as differences in ability to develop a "set" or a "readiness to respond." Insensitivity to changes in foreperiods was found during intoxication. Sensitivity increased after withdrawal of the drug and was apparently normal after three to five months of enforced abstinence.

In view of the observed severe muscular incoordination and lack of ability to acquire and maintain readiness to respond, it was concluded that the general behavior of chronic barbiturate users is very severely impaired. They lack the ability to prepare for and react efficiently in performing manipulative tasks. It appears, moreover, that they could not anticipate emergencies and that they would be very unsafe machine operators.

14. Goodnow and associates have reported that significant deterioration of tapping speed, visual reaction time, naming of opposites, and digit span occurs three hours after oral administration of 0.1 gm. of pentobarbital sodium (Goodnow, R. E.; Beecher, H. K.; Brazier, M. A. B.; Mosteller, F., and Tagiuri, R.: Physiological Performance Following a Hypnotic Dose of a Barbiturate, J. Pharmacol. & Exper. Therap. **102**:55-61, 1951).

CRANIOPAGUS PARIETALIS

Report of a Case

E. GRAEME ROBERTSON, M.D. (Melb.), F.R.C.P., F.R.A.C.P.
MELBOURNE, AUSTRALIA

FEMALE twins, united extensively at the sincipita, were delivered by Drs. W. Smellie and J. Starr,[1] of Wynyard, Tasmania, on March 4, 1950. In their report of the births, the authors stated:

Mrs. E. A. S. was admitted to hospital at 7 p. m. in strong labour. Uterine contractions had begun at 10 a. m. Twins were diagnosed by palpation; the presenting part was a breech. There was considerable delay in the second stage, so the membranes were ruptured and a left foot was brought down. Some time later the right foot presented. Delivery was still delayed. The presentation of a third foot suggested a major complication. On vaginal examination four legs were encountered. To prevent impaction one twin was pushed up beyond the pelvic brim, traction meanwhile being applied to the other. Delivery then proceeded easily. However, attached to the after-coming head was the head of a second twin; the two skulls forming one unit. The twins were very much alive.

There was one placenta and a single amniotic sac. The two cords were attached separately, but close together.

The twins weighed nine pounds eleven ounces. Their length was 33.5 inches. From the left external auditory meatus of one to the right external auditory meatus of the other the distance was 4.5 inches. With the exception of their abnormal junction together at the cranial vaults, they are normal in every respect.

They noted that the mother had five children living and that premature twins had been born dead eight years earlier. The parents were first cousins.

I examined the twins at the Launceston General Hospital, Tasmania, at the age of 11 weeks (Fig. 1). They appeared alert, moved their limbs independently, and slept individually; and their emotional expressions might differ at the same time. One twin (hereafter called Twin 1) took food better and vomited less than Twin 2 and was obviously more active and the larger of the two. The magnitude of the union, involving the whole of the normal vertices, was striking. The distance between the right ear of Twin 1 and the left ear of Twin 2 was considerably greater than the distance between the ears on the opposite side. The lobes of the right ear of Twin 1 and the left ear of Twin 2 (seen on the same side of the conjoint head) were absent and the cartilage of the long lower part of the helix was curved sharply upward, like an inverted U.

X-ray films of the skeletons showed marked asymmetry of the frontal and parietal bones. The metopic (frontal) sutures widened toward the zone of junction and met to form a diamond-shaped fontanelle on the anterior wall of the cranium. The right frontal bone of Twin 1 was considerably larger than the left, and thus the right parietal bone was correspondingly smaller. Similarly, the right frontal bone of Twin 2 was larger, and a triangular projection of the upper and posterior part transgressed the remainder of the line of sutures joining the twins, to articulate between the frontal and the parietal bone of the left side of Twin 1. The occipital bones appeared of normal shape, terminating about 2 cm. above each external occipital protuberance.

Honorary neurologist, Royal Melbourne Hospital and Children's Hospital.

1. Smellie, W., and Starr, J.: M. J. Australia **1**:667, 1950.

From the apices of the occipital bones, and between the posterior edges of the parietal bones there was a very thin layer of bone, apparently representing the disappearing posterior fontanel. No other skeletal abnormality was apparent in complete roentgenograms.

Pneumoencephalography was used to explore the ventricular system when the twins were 11 weeks of age (Fig. 2) and to study the external surfaces of the cerebral hemispheres 6 weeks later. No gas passed from twin to twin. The ventricles appeared normal except for a deficiency in the posterior wall of each third ventricle. In each twin, gas from the third ventricle entered a pocket which extended between the medial surfaces of the parietal lobes, its fundus being in close contact with that of a mirror-image diverticulum in the other twin. The shadows outside the hemispheres suggested that both subdural and subarachnoid spaces existed between the opposing upper surfaces of the right hemisphere of Twin 1 and of the left hemisphere of Twin 2, the smooth upper border suggesting that the separating membrane was probably dura. No certain evidence of a falx existed. On the right side of Twin 2 and the left side of Twin 1 gas collected laterally and the opposing edges were very irregular, suggesting arachnoidal, rather than dural, separation. No gas was seen more medially, its absence suggesting that the medial parts of the superior surfaces of the opposing hemispheres on this side were in close opposition.

Fig. 1.—Photograph of the twins.

Laboratory Studies.—A number of simple investigations were made, which supported the view that the circulations of cerebrospinal fluid were completely partitioned, although some commingling of the blood existed.

Blood Counts	*Twin 1*	*Twin 2*
Erythrocytes	4,610,000	4,438,000
Hemoglobin	55%	55%
Leucocytes	9,000	9,300
Neutrophiles	27%	34%
Eosinophiles	4%	2%
Lymphocytes	55%	59%
Monocytes	14%	5%
Glucose tolerance values		
Fasting blood sugar, mg. per 100 cc.	31	30
10 gm. glucose given to Twin 1		
Blood sugar levels, mg. 100 cc.		
½ hr. after	45	34
1 hr. after	63	40
1½ hr. after	58	38

Indigo-Carmine Test: Two cubic centimeters of solution was injected into a vein of Twin 2. Dye appeared in the first specimen of urine passed by each twin (15 minutes after injection in Twin 1).

Cerebrospinal Fluid: For both twins, the cell count per cubic centimeter was 1 lymphocyte, and the total protein, 45 mg. per 100 cc.

Phenolsulfonphthalein Test: One cubic centimeter of solution was injected into the lumbar subarachnoid space of Twin *2*. Ninety minutes later, there was no dye in the cerebrospinal fluid of Twin 1, but urinary excretion occurred in both.

Course.—At this stage it seemed that any prospect of separation was very poor. It was decided that exploration of the zone of junction on the left side of Twin 1 and the right side of Twin *2* was the next practical step. Consequently, on Aug. 8, both twins were anesthetized

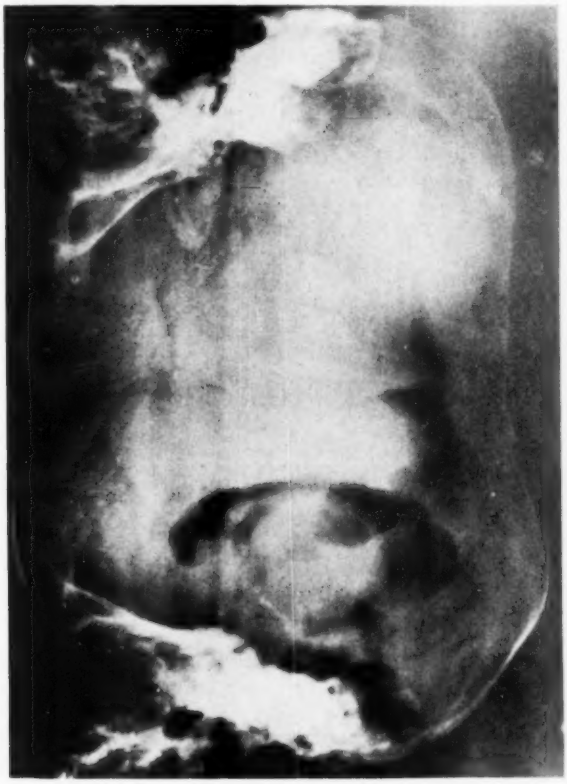

Fig. *2*.—Lateral x-ray film taken after injection of 15 cc. of gas into the lumbar theca of Twin 1.

with cyclopropane, and an endotracheal tube was introduced into each child. Mr. R. S. Hooper, F.R.C.S., made a vertical incision from ear to ear to expose the suture line between the parietal bones of each twin. A burr hole was made through the bone adjacent to the suture line, and this was enlarged until an opening nearly 5 cm. in diameter was obtained. A U-shaped dural flap was then cut. There was no dural separation between the contiguous hemispheres. Small cortical veins from Twin 1 extended upward to join a large arachnoidal vein at least 4 mm. in diameter. On the other side of this vein (i. e., toward Twin 2) there was a large subarachnoid pool, some 1 to 1.5 cm. in depth. The convolutions of Twin *2* formed the floor of this pool, and veins from the cortex extended across the subarachnoid space to the large vein mentioned above. A layer of gelatin sponge was inserted to prevent leakage of cerebrospinal fluid; the dura was closed, and the scalp was sutured in a single layer.

Although the induction of the anesthesia and operative procedure lasted only 35 minutes, the physical condition of the twins showed marked deterioration, indicating that a single-stage attempt at separation would not be tolerated.

Subsequently, carbohydrate intolerance led to loss of weight; and while teething proceeded, the physical condition of the twins was very poor. Measles also led to further deterioration. Any further attempt at separation was considered impractical. At best, by sacrificing Twin 2, a dural flap from the lateral aspect of her right hemisphere might have been reflected medially over the superior hemisphere of Twin 1 and sutured medially to the dural shelf. There would, then, have been a very large area of dura to be covered by skin flaps. The venous communications would have prolonged the operation, and their blockage might have led to cortical infarcts. In their deteriorating condition it was believed that the infants would not survive even minor operative intervention, let alone such a major procedure.

Because of the possibility of separation when the death of one twin seemed imminent, Mr. Hooper performed an angiogram to determine the venous drainage of the hemispheres of the stronger twin.

Twin 1 was anesthetized with cyclopropane, and an endotracheal tube was inserted and cyclopropane and oxygen anesthesia continued. After a preliminary intradermal test, the left internal carotid artery of Twin 1 was exposed and a test injection of 8 cc. of 25% iodopyracet (Pyelosil) was made, without untoward result. The same amount of 35% iodpyracet was then injected, and eight anteroposterior films were taken during the next seven seconds.

At the conclusion of the injection there was pronounced flushing of the face on the side of injection and the child made a deep inspiration, after which there was no spontaneous respiration. The cyanotic skin became of a gray hue, and no pulse or cardiac impulse could be detected. After some delay, intracardiac epinephrine was given; but as this failed to stimulate the cardiac muscle, an upper abdominal incision was made and cardiac massage commenced. After 20 to 30 seconds a few irregular contractions occurred, and a regular rhythm was soon established. Subsequently, respirations commenced spontaneously.

The first film showed the proximal parts of both anterior cerebral and both middle cerebral arteries. The left posterior communicating artery and part of the basilar artery were seen. The filling of all vessels increased during the next second, the whole of the basilar artery and the two vertebral arteries being evident (Fig. 3*A*). No posterior cerebral arteries were seen. In subsequent films the filling of the left middle cerebral artery regressed (Fig. 3*B*), so that the larger distal branches, which had previously been seen, no longer filled and only the poorly filled proximal part was seen. In contrast, the right middle cerebral artery and the anterior cerebral arteries were well filled. During the fifth second, arteries were still to be seen in the periphery of the right hemisphere, together with a diffuse shadow suggesting filling of small vessels on this side, but no corresponding filling occurred on the left, the side of injection. The left internal carotid artery and the basilar artery were still filled. In the next films the veins on the right side were seen to be filling, and the basilar shadow disappeared. At the end of seven seconds only veins and the genu of the left internal carotid artery were seen.

Thus, the cerebral circulation was extremely slow, largely due to failure in cardiac output. The poor filling of the smaller branches of the middle cerebral artery on the side of injection suggested that these arteries presented more resistance to flow than others, and their early disappearance suggested the possibility of arterial spasm. The filling of the basilar artery indicated that the resistance to retrograde passage into this large artery was less than that into the posterior cerebral artery and, less directly, into other cerebral arteries. This condition may be ascribed to arrest of cardiac activity, possibly with spasm of vessels.

For several days Twin 1 remained unconscious, and she became, and remained, the smaller twin, leading to a striking reversal of the previous appearance. As she became more conscious, extensor rigidity slowly developed, first in the left upper limb, then in the right limbs, and finally in the left lower limb. Fifteen days after the angiograms were taken Twin 1 was in a state of decerebrate rigidity. The plantar responses were of extensor type. The temperature of each twin was elevated, and, although the charts were more or less parallel, the temperature of Twin 1 was usually higher than that of Twin 2. Finally, on the night of Jan. 4, 1951, the temperature of Twin 1 reached 106 F., and that of Twin 2, 105 F. Twin 1 then suddenly vomited

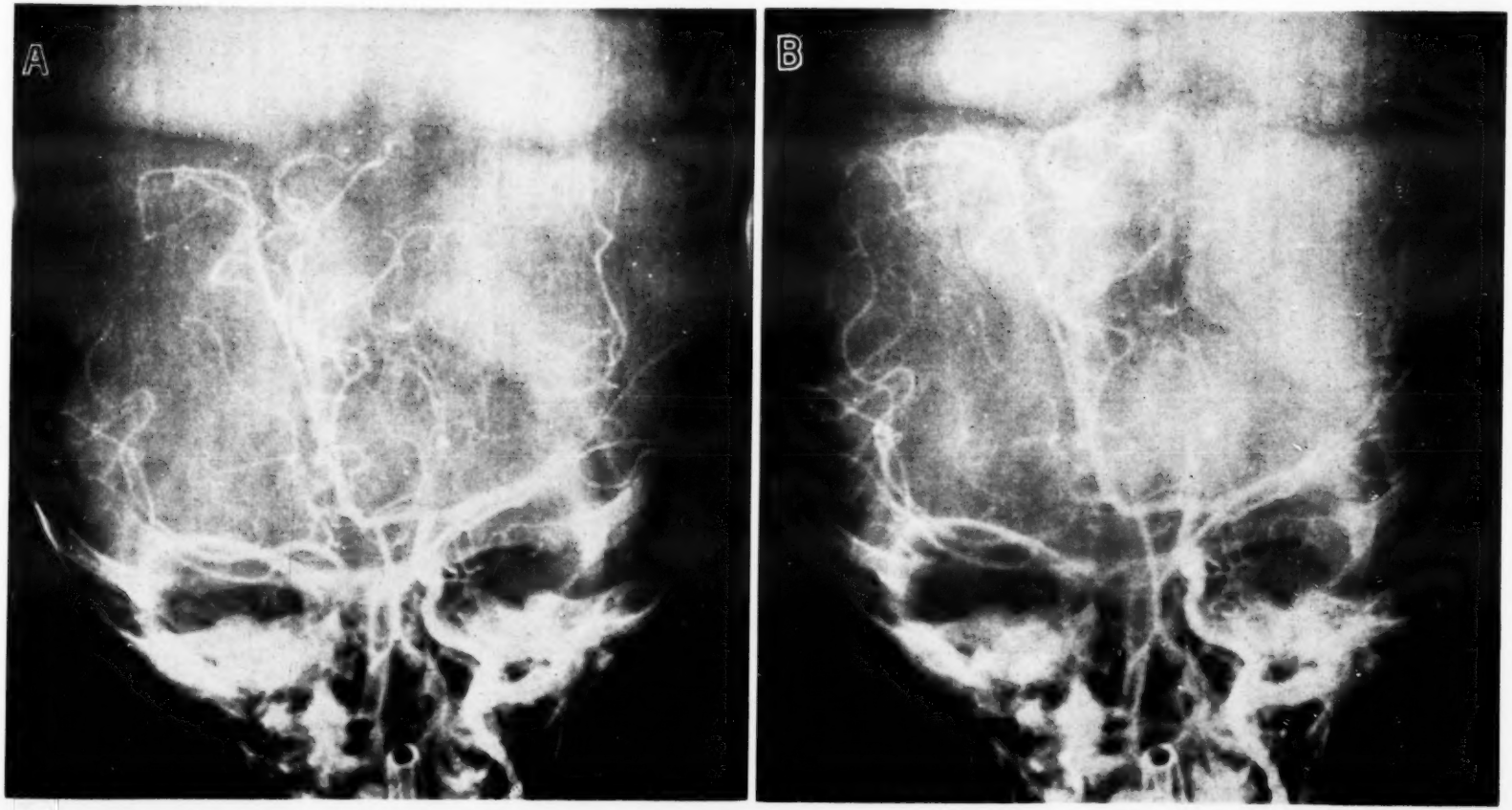

Fig. 3.—Left carotid angiogram of Twin 1. *A*, early film, showing anterior and middle cerebral arteries on both sides and basilar and vertebral arteries. *B*, film one second later, showing regression of filling of left middle cerebral artery, while that on the opposite side continued to increase.

coffee-ground material and died immediately afterward. Twin *2* died within five minutes. The death of the second twin so soon after the first is probably evidence of the extent of the circulatory anastomosis, the living twin bleeding into the vessels of the other.

Postmortem Examination.—Postmortem examination of the twins revealed the presence of miliary tuberculosis, and this may be presumed to have been a contributory cause of death. The posterior parts of the lungs of Twin 1 showed pneumonic consolidation, with tubercles on microscopic examination. The lungs of Twin *2* showed merely edema. No miliary tuberculous infection was noted in the central nervous system, and description of the necropsy will be limited to the structure of the brain and its coverings. No developmental anomalies were found in the viscera.

Fig. 4.—Internal aspect of dura over the posterior aspect of the two brains.

The conjoint skull was cut from foramen magnum to foramen magnum along lateral lines, which reached as far forward as the mastoid processes. The bone was densely adherent to the dura, especially along the suture lines. It was possible to separate the loosened bone from the dura, but further progress in removal was possible only after the dura had been incised along the line of bony division. Thus, dura was left over the brains posteriorly, but the rest of the brain was separated from its dural covering. The tentoria were incised close to their bony attachments (along the petrous portions of the temporal bones).

The posterior dura, which was removed *in situ*, was thick near the median plane and contained many venous sinuses. On the cerebral side (Fig. 4) two vertical folds, *2* cm. deep, were seen. These folds ran in uninterrupted fashion across the zone of junction, being continuous from twin to twin. They were placed more or less symmetrically on each side of the median plane, about *2* cm. apart. Cranially the two folds lay between the widely separated medial surfaces of the occipital lobes of each twin (Fig. 5). Inferiorly they diverged between the corresponding inferomedial surface of the temporal lobe and the superior surface of the cere-

bellum and terminated by attachment along the petrous portion of the temporal bone. At the level of the apex of the cerebellum of each twin the dura between the folds was heaped up into a small ridge. Laterally on each side it merged into the base of the corresponding vertical fold as the latter swung outward between the temporal lobe and the cerebellum. The ridge was thickest at its apex, where it was pierced by the great cerebral veins. A small fold of dura, the falx cerebelli, ran downward from the apex, soon losing its identity in the posterior dura. Venous sinuses ran along the bases of all folds. In terms of normal development, the ridge seemed to represent, in rudimentary fashion, the central portion of the tentorium. More definitely, the diverging portions of the vertical folds represented the lateral portions of the tentorium. The parallel portions of the vertical folds gave the impression of being a bifid posterior part of the falx, which, however, lacked any connection with the anterior falx.

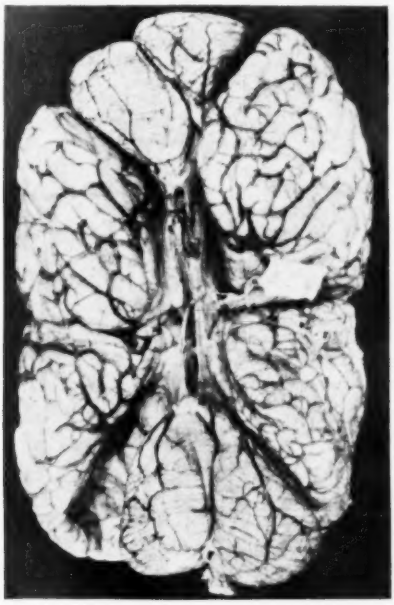

Fig. 5.—Posterior aspect of the two brains (Twin 1 below).

Study of the lateral aspects of the brains showed a shelf-like process of dura extending from the lateral wall of the skull to the median plane, between the right cerebral hemisphere of Twin 1 and the left cerebral hemisphere of Twin *2* (Fig. 6*A*). Posteriorly it fused wth the previously described vertical fold on the near side. From the median free edge of the anterior part of this shelf a falx extended downward between the frontal lobes of Twin 1 (Fig. 6*B*). It curved in front of the genu of the corpus callosum, to be attached to the crista galli, below. There was no true falx posteriorly, nor was there any dural partition between the two hemispheres of Twin *2*. There was no dural partition between the left hemisphere of Twin 1 and the right hemisphere of Twin *2* (Figs. 5 and 6*B*). The superior surfaces of these hemispheres were in close apposition but could be separated. Anteriorly and posteriorly the plane of cleavage was more clearly defined than laterally, where horizontally directed veins concealed the joined edges. (The largest of these veins was that seen during the operative exposure.) The gyri of each twin interdigitated to a considerable extent, and could be separated after the arachnoidal membrane on the surface and the many web-like filaments of fibrous tissue running between the two hemispheres were torn.

It may be remarked at this point that the lateral aspect of the combined hemispheres was deeper (from base to base) on the side with the dural shelf than on the side without. This corresponded with the greater ear-to-ear distance on the right side of Twin 1.

The anterior, posterior, and superior surfaces of the brains were flattened. This squaring-off of the hemispheres led to distortion of the normal pattern. The frontal and temporal lobes made up a very large portion of the lateral aspects of the hemispheres. The parietal lobes contributed only a small triangular area, most of the parietal cortex being on the superior surface. The occipital lobes appeared deep, but small, in anteroposterior extent. The usual major convolutions could be distinguished, although there was a great deal of asymmetry (compare the callosal and cingulate gyri in Figure 8). The ascending frontal convolutions were interrupted by trans-

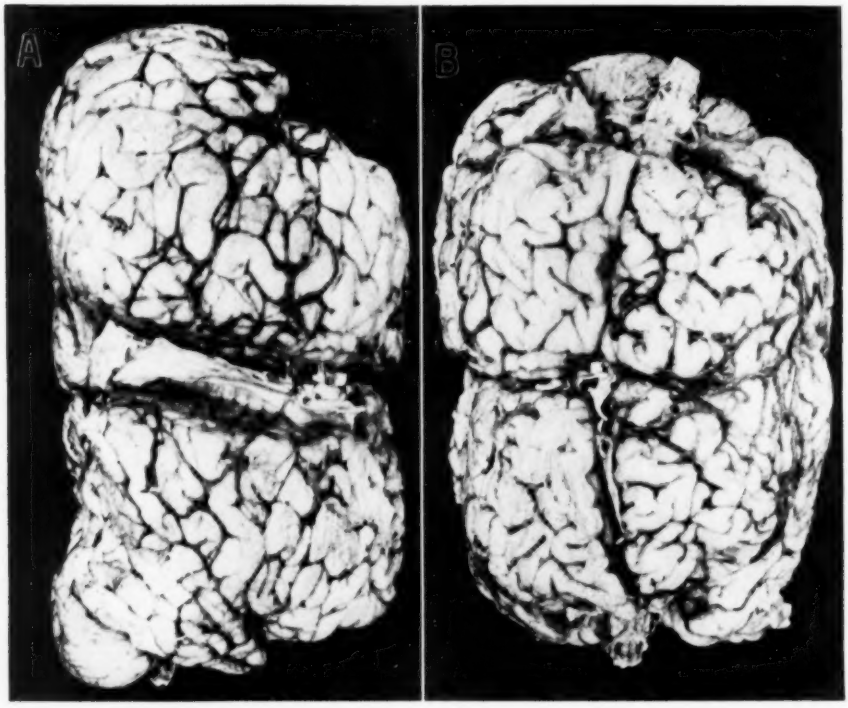

Fig. 6.—*A*, lateral aspect, right side of Twin 1, left side of twin 2. *B*, anterior aspect.

verse sulci. It is possible that much of the convolutional asymmetry was due to distortion of pattern caused by varying degrees of pushing together of the hemispheres. A full description of the convolutional pattern would be unduly tedious.

The left temporal lobe of Twin 1 was atrophic, and its fluctuant nature suggested that the temporal horn of the left lateral ventricle was widely dilated. The posteroinferior part of the lateral aspect of the parietal lobe and the lateral aspect of the occipital lobe were also atrophic.

As previously mentioned, the short, but deep, occipital horns of each twin were widely separated. Between the medial surfaces lay the vertically directed dural folds, the free edges deeply notching the medial surface of the right occipital lobe of Twin 1 and (less deeply) the right occipital lobe of Twin 2 (Fig. 5). The arrangement of dural folds, diverticula, occipital lobes, and cerebellums is illustrated diagrammatically in Figure 7. Bridging between the medial aspect of the lobes and the apex of the cerebellum of each twin were rather dense membranes,

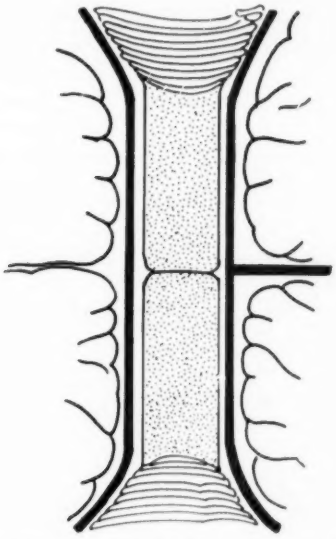

Fig. 7.—Diagram showing arrangement of dural folds: diverticula, posterior poles of cerebral hemispheres, and cerebellum, as seen from behind.

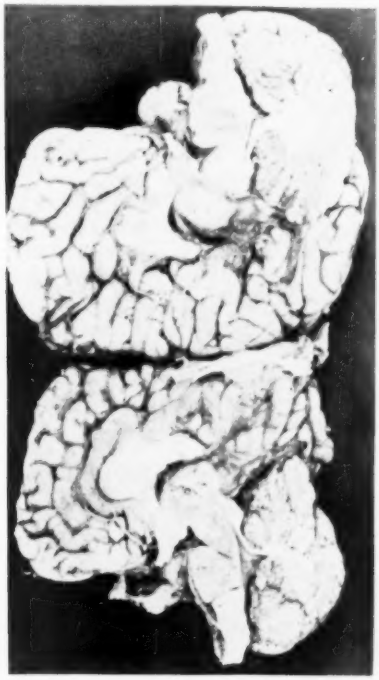

Fig. 8.—Median sagittal section of hemispheres (Twin 1 below).

which formed the posterior walls of the pockets seen in the encephalograms. Incision of these membranes revealed cavities which extended approximately 2.5 cm. forward between the hemispheres, being limited by approach and adhesion of the lateral walls. The cavity of Twin 1 was wider than that of Twin 2. Above, the cavities were separated by a thick membranous partition. The medial edge of the dural shelf, with its accompanying sinus, abutted upon the right lateral wall of the pocket (with reference to Twin 1). Inferiorly the pocket was limited by cerebellum, and anteroinferiorly it could be seen running into the third ventricle.

Median sagittal section of the hemispheres (Fig. 8) showed that the pocket opened widely into the posterior part of the third ventricle. A small lens-shaped white mass on the inferior wall of the pocket, just behind the posterior commissure, seemed to represent the pineal gland, and section showed it to consist of glandular tissue. Choroidal tissue formed on the lateral walls just above and behind the third ventricle and ran forward into the velum interpositum. Microscopically, the limiting membrane was formed of fibrous tissue, lined internally by cuboidal cells, which appeared identical with ependymal cells. Thus, the relation to the third ventricle, the position of the pineal gland, and the cellular structure of the membrane suggested that the pockets were formed by expansions of the posterior wall of the third ventricle above the pineal gland. The third ventricle appeared to be normally formed in other respects. Twin 1 had a large massa intermedia; Twin 2, none (Fig. 8). The genu of the corpus callosum was bulky. The body was short but thick. It extended only 1.5 cm. dorsal to the foramen of Monro, where a well-defined splenium was seen. The cross section of the corpus callosum was considerably smaller in Twin 1 than in Twin 2. The fornix seemed to be well formed.

The shape of the cerebellums was unusual. Their posterior aspects were triangular, with an acute angle superiorly. The left lobe of Twin 1 and the right lobe of Twin 2 (to a less extent) were longer than the corresponding opposite lobes. The apex of the cerebellum of Twin 1 was formed by the medial portion of the left hemisphere, and of Twin 2, by the right hemisphere. The cerebellum was of small anteroposterior diameter. The pons and the medulla were of normal anatomical outline.

The aqueduct of Twin 1 was of normal caliber; that of Twin 2 was narrowed to a small chink in its lower part. It was, however, patent, and there was no evidence of surrounding gliosis.

Finally, there was striking asymmetry of the circles of Willis (Fig. 9). In Twin 1, the anterior, middle, and posterior cerebral arteries arose from the carotid artery. The proximal part of the left anterior cerebral artery was much larger than the right and, through a large, single anterior communicating artery, supplied most of the blood to the large distal part of the right anterior cerebral artery. Small posterior communicating arteries ran between the posterior cerebral arteries and the superior cerebellar arteries. In Twin 2, the usual arrangement of basal vessels was present. This asymmetry and the presence of an infrequent, but well-known, developmental anomaly in one of the two identical twins, were unexpected. It is probable that unusual conditions (perhaps a pressure effect) upon the developing arteries may determine variations which are not genetically installed. In turn, this may have a bearing upon the explanation of such anomalies in more normal persons. However, it is also to be remarked that the corpus callosum was larger in Twin 1, and, more striking still, there was a massa intermedia in Twin 1 and not in Twin 2.

DEVELOPMENTAL CORRELATION

The material does not warrant an expression of opinion regarding the mechanism of such twinning. The final structure is not a definite guide to the process of development. The same result may have been produced whether fission or fusion was responsible. The incomplete separation of two cellular masses, arising from fertilization of a single ovum, the development of two organizing centers (in a single cellular mass) with an overlapping influence, or the pressing together at the future cephalic ends of two cellular masses, which had initially separated, might

be evoked. The first two explanations seem the more probable.[2] Another explanation involves fission at a later stage of development, but seems much less likely. It has been suggested that splitting of a single embryonic disk occurs along the line of the primitive streak. If the separation of the two halves is incomplete at the cephalic end, craniopagus might result. If this is to explain craniopagus parietalis, however, twins which originally lay side by side would have to separate into the end-to-end position. The twins would be expected to be mirror images, and variations in structure of one would be more likely to be reproduced in the other than if the partial separation occurred earlier.

In whatever manner the twinning arose, however, the disposition of the diverticula of the third ventricles and of the membranes covering the brain allowed of certain deductions as to their origin. In this particular instance it is apparent that the abnormality is to be sought at the head end of each embryo. In the early stages

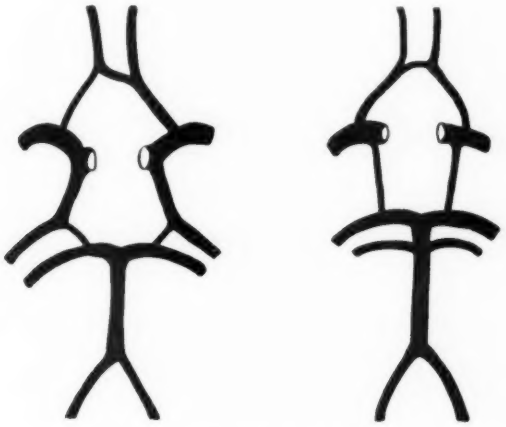

Fig. 9.—Circles of Willis.

of development the dorsal wall of the prosencephalic cavity forms the most cranial part of the embryo. The cerebral vesicles bud out from each side of the cavity, and the further development of the cerebral hemispheres causes the original cavity to sink caudally as it acquires the normal form of the third ventricle. If, at an early stage, the neighboring roofs of the prosencephalic cavities of two twins became firmly adherent, the roofs could become drawn out into diverticula as the massive cerebral hemispheres expanded laterally and above. A study of a diagram of 25 mm.

2. In the first two conditions the twins would be monozygotic, as they would probably be in the third. Gruenwald (Arch. Path. **44**:495, 1947) pointed out that the state of the membranes is no guide to whether the origin is from one or two ova. He stated that if possibilities detailed by Grevlich exist, "monozygotic twins could have all possible relations of their membranes, including separate chorions, which are often assumed to be proof of dizygotic origin. This, together with the fact that the chorions of dizygotic twins may fuse secondarily into one, shows that the membranes cannot be relied on in the determination of the type of twinning in a given case."

embryos (Hochstetter, 1919) shows that the diverticulum would open into the third ventricle between the dorsal end of the corpus callosum and the pineal body (Fig. 10). The diverticulum itself would lie between the medial surfaces of the cerebral hemispheres. Situated in this region, the diverticulum might well interfere with the normal backward displacement of the occipital lobes and would tend to force them

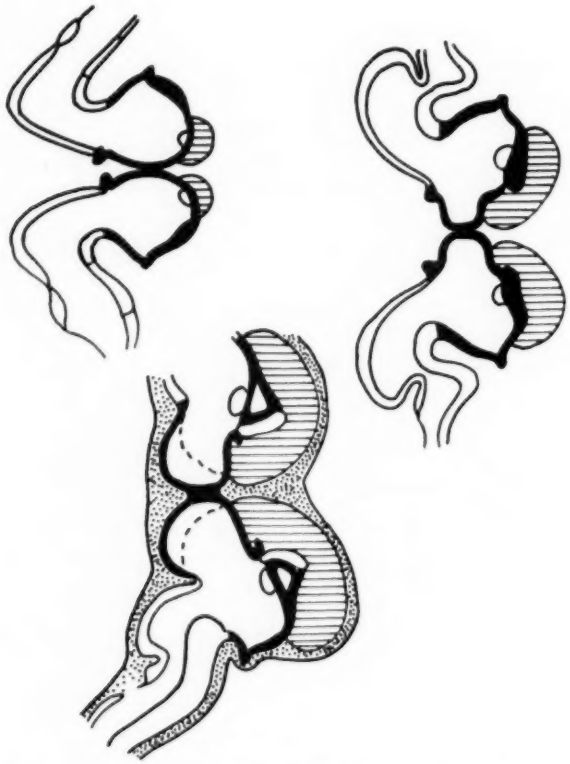

Fig. 10.—Three stages of development of anterior parts of neural tubes. Adhesion between the cranial parts of the two apposed prosencephalic cavities causes drawing out, as each third ventricle is submerged by the expanding cerebral hemispheres, of what should become the posterior wall of the ventricle.

The prosencephalic cavity has a solid-black surround; the cerebral hemispheres represented by horizontal hatching, and mesenchymal primordium of the meninges is shown as dotted.

The drawings are based upon diagrams of sagittal sections through the brains of human embryos, 3.2, 25, and 65 mm. long; modified from Hochstetter by W. J. Hamilton, J. D. Boyd, and H. W. Mossman (Human Embryology, W. Heffer & Sons, Ltd., Cambridge, England, 1945).

laterally. Thus, the shape of this part of the brain would be altered. The posterior part of the third ventricle would lie nearer the occipital bone than usual. This might result in narrowing of the anteroposterior diameter of the cerebellum, with a corresponding increase in its craniocaudal extent.

At an early stage mesoderm proliferates around the neural tube and later divides into outer and inner layers. The outer layer differentiates into bone and dura; the inner, into arachnoid and pia. The dura apparently forms by condensation around the brain and between major subdivisions. The changes in shape of the developing brain results in infolding or ingrowth of the membranes between the two cerebral hemispheres and between them and the cerebellum. In the instance being considered, fundal adhesion between the diverticula would prevent the ingrowth of mesoderm; hence no meninges would develop between them. Unequal apposition of the developing hemispheres of the two twins (with unequal degrees of pressure, possibly due to posture of the twins *in utero*) might account for the uneven development of meninges on the two sides. Where the superior surfaces of the hemispheres were closely applied only pia-arachnoid developed; where the surfaces lay apart dura was laid down. (It may be recalled at this point that the distance of the ear of one twin from that of the other was considerably greater on the side possessing the dural shelf than on the other.)

Posteriorly the presence of the diverticulum between the medial surfaces of the hemispheres would leave no room for normal development of the falx. However, between the posterior part of the sacs and the widely separated occipital lobes there was considerable space, and in this space dura could develop (Fig. 5). The dorsal surface of the joined diverticula was continued across the zone of separation, owing to the fundamental process of adhesion. Hence the two parallel dural folds (Fig. 4), lying one on each side of the diverticulum, between it and the occipital lobe on each side and running in uninterrupted fashion from twin to twin, may be readily explained (Fig. 7). Caudally, the diverticulum is adherent to the apex of the cerebellum, and the gutter on each side of the diverticulum runs into the space between the corresponding temporal lobe and the superolateral surface of the cerebellum (Figs. 5 and 7). This may account for the continuity of the folds from the petrous portion of the temporal bone of one twin to that of the other.

The lack of development of a normal, shelf-like tentorium may again be due to the presence of the diverticulum, adherent to arachnoid at the apex of the cerebellum close to the occipital bone. There was no room for the usual dural condensation, but merely space for a low, hillock-like proliferation of the dura of the dorsal wall of the skull. On the other hand, this may be due merely to underlying veins. The diverticula would probably lie closer to the dorsal wall of the cranium at an earlier stage than later, when the occipital lobes reached their fullest development.

Finally, it may once again be pointed out that none of the posterior dural partitions fused with the incomplete falx, lying between the anterior parts of the hemispheres.

McNaughton [3] and Penfield and McNaughton [4] have shown that the nerve supply of the dura and sinuses of the posterior fossa arises chiefly from the vagus nerve, with the addition of fibers from the hypoglossal, and possibly the glossopharyngeal, nerve. The upper surface of the tentorium and the posterior part of the falx are supplied on each side by a branch of the first trigeminal division, the nervus tentorii. The anterior part of the falx, however, has an entirely different nerve supply from the anterior and posterior ethmoidal nerves, which come from the

3. McNaughton, F.: A. Res. Nerv. & Ment. Dis., Proc. **18**:178, 1938.

4. Penfield, W., and McNaughton, F.: Arch. Neurol. & Psychiat. **44**:43, 1940.

first division of the trigeminal nerve. The authors pointed out that this difference in nerve supply of the anterior and the posterior part of the falx has a close developmental parallel, for, according to Markowski,[5] these portions of the falx develop separately, and later unite.

Markowski [5] studied serial sections of 11 embryos at different ages. He stated that the anterior part of the falx first appears on the base of the skull anteriorly and grows in a dorsal direction. The posterior part of the falx develops along with the tentorium. The anterior and posterior parts of the falx, developed separately, later join to form the normal falx. In a painstaking piece of work, he showed that the first anlage of the tentorium develops as a transverse folding of all three membranes of the brain in connection with the acute folding of the brain above the "middle cross piece" of the base of the skull, i. e., the portion of the base which forms the sphenoidal (pterygoid) ridge and the petrous part of the temporal bone. On each side, the upper part of the fold is attached in front to the lesser wing of the sphenoid, and the lower part, to the petrous portion of the temporal bone, recurving below to line the posterior fossa. The two layers join in the midline in front of the developing brain stem and then grow backward around the brain stem, to join behind it. It becomes continuous with the dura over the cranial bones. While this is occurring, the cerebral and cerebellar hemispheres are rapidly expanding, so that the upper and lower layers of the fold are pressed together to form the falx. The part anterior to the petrous portion of the temporal bone is no longer part of the falx but lines the floor of the middle fossa. The brain stem is thrust forward by the development of the occipital and cerebellar lobes, thus leading to the disappearance of that part of the primitive falx near the midline anteriorly. From the superior lamina of the tentorium the posterior part of the falx develops, growing forward between the two hemispheres, and eventually fuses with the anterior part of the falx.

Thus, this study throws light even on the difference in nerve supply of the upper and the lower part of the falx. The correlation with the developmental explanation (made before the work of Markowski and of Penfield and McNaughton was known to me) is self-evident. The presence of the diverticula prevented the junction of the two halves of the tentorium in the median plane behind the mesencephalon; hence the tentorium remained in two halves. Each half contributed its own posterior part of the falx, and possibly the arrangement of gutters on each side of the diverticula contributed to the final form. The apposition of diverticulum and medial surface of the cerebral hemispheres prevented forward growth of the posterior part of the falx; hence no union occurred between the separately developed anterior and posterior parts.

REVIEW OF RELEVANT LITERATURE

The lesion is a rare one. Keevil [6] stated that Mall had computed that 7% of all pregnancies terminate in aborted pathological ova and about 0.6% in malformed fetuses at term; of the latter only a small proportion are conjoined twins (of all types). In 100,000 pregnancies, Puech found 517 malformations of various types, but only 2 were double monsters (none being of the type here described). Schole-

5. Markowski, J.: Ztschr. ges. Anat. **94**:395, 1931.

6. Keevil, N. L.: J. Obst. & Gynec. Brit. Emp. **52**:513, 1945.

field [7] stated that "the rarest type of double monster is that in which the axes of the two individuals are placed end-to-end." It is to this group that cases of craniopagus parietalis belong.

The total number of recorded cases of joined twins is not large, but the cases collected by Tartuffi show the relative frequency of each.

Thoracopagus	86
Pygopagus	22
Ischiopagus	7
Craniopagus	2

Trenkner [8] stated that Förster [9] compiled 15 cases of craniopagus in 1865, in 9 of which the union was parietal. In 1909 Warschauer collected 21 cases, 2 of the frontal, 14 of the parietal and 5 of occipital type. Trenkner was able to add eight cases of craniopagus parietalis, although he could not consult all original references. The first case was observed in 1495 by Münster; hence the collection covers 450 years. I have found no additional descriptions. However, as always, the literature is not a true guide to frequency, for even such a rare anomaly may escape description. While recently in the United States, I heard of two cases (one Negroid) in which the twins were then living. In no case was the abnormality diagnosed before birth; indeed, twinning was usually unsuspected. As a rule the twins died in the first week. In the case of one set life was prolonged to the age of 10 years, all the other twins dying in the first year of life.

The drawings and photographs in the articles which I have been able to consult show a remarkable similarity in appearance of the twins. The long axes were usually inclined at a small angle, and sometimes there was slight rotation of the axes. Thus, the twins face more or less in the same direction and the bodies lie along the same line. In a case described by Dabelow [10] the angle between the axes was so great (the distance between the ears being so much greater on one side than the other) that lateral flexion of the necks permitted the bodies to lie parallel. In a case described by Löwenberg [11] the children faced in opposite directions. (The right parietotemporal region of one had fused with the right parietal region of the other. The dura showed no malformation except for an opening in the parietal region corresponding to the defect in the skull. The convolutional pattern and the microscopic appearance of the cortex suggested that development had reached that of the eighth month of intrauterine life. Löwenberg assumed that limitation of space interfered with further convolutional development. He believed that the fusion of the skulls was a late malformation. This is probably a different type of anomaly from true craniopagus parietalis.) In many cases other minor developmental anomalies existed, and deformity of two neighboring ears was present in a considerable proportion of cases. However, other deformities were few and slight, except

7. Scholefield, B. G.: J. Anat. **63**:384, 1929.

8. Trenkner, W.: Beitr. path. Anat. **101**:223, 1938.

9. Förster, A.: Die Missbildungen des Menschen systematisch dargestellt, Ed. 2, Jena, F. Mauke, 1865.

10. Dabelow, A.: Anat. Anz. **62**:133, 1926.

11. Löwenberg, K.: Am. J. Path. **6**:469, 1930.

in the case described by Kafka,[12] in which there were many deformities of the pulmonary, urinary, genital, and alimentary systems, including eventration and atresia ani in both twins.

Postmortem descriptions are lacking or poor. In all instances examined the brains were separate, and except in one specimen dura intervened between the hemispheres on one side only. As an example, the case described by Otto[12a] may be mentioned. The monster was born at the fifth month and consisted of two female fetuses joined by the vertices. Their axes are described as "slightly twisted on one another. There was no nervous continuity." The bones at the vertex were wanting, and the underlying dura mater was also deficient over one hemisphere. On the opposite side, a single layer of dura separated the two brains. On the side where the dura was deficient the hemispheres were flattened against one another, but there were a distinct arachnoid membrane and a separate subarachnoid space for each fetus.

Blumensaat[13] described a case in which there was no dura between the hemispheres. The description merits recapitulation. The female twins were born without medical aid, the feet of one presenting first. One twin died three days after birth, with gastrointestinal symptoms and extensive pneumonia. Within 12 hours the second twin became febrile and restless. In order that it might be determined whether separation was possible, 70 cc. of air was blown into the cisterna magna of the dead twin. An apparently common air space, 11 cm. long by 2 cm. wide and 2 cm. deep, was seen in the midplane posteriorly. This was taken to indicate that the twins had a common subarachnoid space; hence no attempt at separation was made. The second twin died 24 hours after the first. After death suboccipital injection of gas in the second twin showed an appearance similar to the earlier roentgenograms. After the cranium was opened, the suspected dural lining of the common space was observed, but there was no dura between the two brains, their surfaces being in intimate contact and separated only by pia. In the longitudinal fissure of each brain there was a moderately high falx, which was not united with the falx of the opposite brain. Posteriorly the falx was doubled in each cranial cavity. The tentorium had a gap in the form of an oblong wedge, increasing in size from front to back. At the free borders of the tentorial gap the falx started. In this doubling of the falx there was no brain substance, but the space so formed belonged, it was thought, to the subarachnoid space seen in the encephalogram. Thus, the arrangement was very similar to that seen in the present case, although the significance of the median air shadow was not recognized. The interval between the death of the two twins is interesting and suggests that there was less vascular anastomosis in this case than in others, for the short period between deaths in others may have been due to the living twin bleeding into the dead one.

Attempts were made to separate the infants in several instances. Apparently, priority goes to Münster, in 1945! In 1929 an attempt at separation was made in a case of which two descriptions are provided, one by Cameron[14] and one by Scholefield.[7] Two complete female infants were joined together by the whole extent

12. Kafka, V.: Ztschr. angew. Anat. **5**:185, 1919.

12a. Otto, A. G.: Monstrorum sexcentorum descriptio anatomica 1841, Vratislaviæ, F. Hirt, cited by Scholefield, B. G.: J. Anat. **63**:384, 1929.

13. Blumensaat, C.: Arch. path. Anat. **285**:140, 1932.

14. Cameron, H. C.: Lancet **1**:284, 1928.

of the vertex of the skull. One twin (A) was somewhat larger, of better color, and generally stronger and more active than the other (B). The axes of their bodies inclined at an angle of about 15 degrees, and there was a slight degree of rotation of the axis of one on that of the other. There were two independent umbilical cords, but a single placenta. When it became obvious that Twin B was unlikely to survive, an attempt was made, on the 12th day of life, to separate the twins. It was hoped that Twin A would thus be saved. When the subdural space of Twin B was opened, the pulse of Twin A suddenly failed, and death was instantaneous. Postmortem examination showed that the folds of dura were completely developed on the left side of Twin A and on the right side of Twin B, the falx cerebri being well formed in each. On the right side of Twin A and the left side of Twin B the dura mater was defective, so that the corresponding hemispheres of the two infants were only separated by pia mater. Unfortunately (beyond a brief reference to the superior longitudinal sinuses), no more detailed description of the brains and membranes is given.

Leiter [15] described an attempt to separate twins who were born by Caesarian section. Interesting medicolegal problems were raised. The father requested that both children be allowed to die, but this was refused. He then requested that an attempt at separation should be made. It was decided that only one could be saved because of the large bony defect which would remain. However, even with the approval of the father, killing one to save the other was homicide according to German law. However, it was decided that it could be said that such a double malformation was not two human beings, but one monster from which a normal human being could be formed. Signs of hydrocephalus (separation of sutures) were found at six days; hence it was decided to proceed by sacrificing the twin with a distorted neck. On the eighth day of life a circular skin incision was made above its eyes and ears and the cranial cavity laid open. The brain of that child was removed. It was found that only on one side did a sickle-shaped dural fold separate the two brains. On the other side the two brains had grown together, and there were extensive confluences of veins. After the separation both children died, as the author states was bound to occur because of the condition found. Permission was given for the use of one body only for scientific purposes. Only polydactyly was found.

In 1100, the surviving Biddenham twin refused an attempt at separation from her dead sister, to whom she was united by the shoulder and hip, saying, "As we came together, we will also go together." [16] These words of simple dignity, worthy to rank among famous last words, seem to epitomize the fate of craniopagus parietalis. Happily, this tradition has since been broken by the planning, judgment, and skilful effort of Dr. Oscar Sugar and his colleagues, in Chicago

My colleague, Mr. R. S. Hooper, F.R.C.S., cooperated in this study.

15. Leiter, K.: Zentralbl. Gynäk. **56**:1644, 1932.

16. Ballantyne, J. W.: Manual of Antenatal Pathology and Hygiene: The Embryo, Edinburgh, W. Green & Sons, 1904.

SOURCE AND NATURE OF NERVE FIBERS IN CAT CORNEA

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IT IS GENERALLY accepted that the cornea is supplied entirely by pain fibers from the ophthalmic division of the trigeminus. Less well known are the various conceptions and arguments put forward as to their other sources and functions, i. e., that the maxillary division supplies the lower half of the cornea (Jefferson[1]), that autonomic fibers coexist with the sensory (Behr,[2] Knapp,[3] Dandy,[4] Boeke,[5] Nageotte and Guyon,[6] and Marchesani[7]), that large multipolar nerve cells are occasionally present (Zander and Weddell[8]), and that, in addition to pain, the modality of touch exists (Rowbotham[9]; Grant, Groff, and Lewy[10]; Tower,[11] and others).

My colleagues and I undertook the experimental studies to be described here in the hope that further light might be thrown on these questions.

EXPERIMENTAL INVESTIGATION

Methods.—Intracranial division of the ophthalmic, maxillary, and oculomotor nerves was performed successfully on 14 cats, and cervical sympathectomy on *2* cats. Operations on five other cats were failures.

The weights of the animals ranged from *2* to 5 kg.

The anesthetic of choice was chloroform, which was administered from a Boyle machine. Trichloroethylene (Trilene) was also used, but the level of anesthesia was not as easily maintained as in the case of chloroform.

The ophthalmic and maxillary nerves were divided under direct vision extradurally. Division of the oculomotor nerve, however, was performed intradurally and proved to be a difficult operation, for it is possible to get only fleeting glimpses of the nerve as it crosses from the brain stem to the sphenoid sinus.

From the Department of Physiology, King's College Medical School, University of Durham.

1. Jefferson, G.: Brit. M. J. **2**:309 and 879, 1931.
2. Behr, C.: Ztschr. Augenh. **62**:1, 1927.
3. Knapp, P.: Klin. Monatsbl. Augenh. **82**:241, 1929.
4. Dandy, W.: Bull. Johns Hopkins Hosp. **36**:105, 1925.
5. Boeke, J.: Ztschr. mikr.-anat. Forsch. **38**:594, 1935.
6. Nageotte, J., and Guyon, L.: Comp. rend. Assoc. anat. **33**:369, 1938.
7. Marchesani, O.: von Graefes Arch. Ophth. **148**:187, 1948.
8. Zander, E., and Weddell, G.: J. Anat. **85**:68, 1951.
9. Rowbotham, G. F.: Brain **62**:364, 1939.
10. Grant, F. C.; Groff, R. A., and Lewy, F. H.: Arch. Neurol. & Psychiat. **43**:498, 1940.
11. Tower, S. S.: J. Neurophysiol. **3**:486, 1940.

All the animals were nursed in padded cages to prevent postoperative injury. They were killed under ether anesthesia at different times, ranging from 6 to 21 days after operation.

Routine Clinical Examination.—After operation, routine examinations were performed daily until the cats were killed. In the first seven animals central tarsorrhaphy (Pomfret-Kilner technique) was performed, but it was found that the procedure was unnecessary. The uncovered eyes, washed out every second day and bathed with cod liver oil, did not ulcerate. The routine examination of the eyes included the following items: (1) general condition; (2) state of wound; (3) pupils, (*a*) diameter and (*b*) response to light; (4) cornea, (*a*) haziness, (*b*) staining with fluorescein, and (*c*) response to strand of lint; (5) ocular movements (third, fourth, and sixth cranial nerves).

After the final examination, before the cat was killed, under general anesthesia, the various responses of the cornea to the strand of lint were charted. The response classified as Type A was the normal response, painful to the animal, and generally causing it to struggle. That classified as Type B describes a less painful response, although the stimulus was obviously felt: The animal moved its head but without any evidence of discomfort.

Technique Employed to Stain the Nerve Fibers.—Prior to the experiments the vital staining of the corneal nerve fibers with methylene blue was practiced in the manner described by Weddell and Zander.[12] The supravital staining technique was chosen in preference to the intravital method, as it was found to be more reliable. In the wide range of laboratory cats used, the corneas exhibited an equally wide variation in thickness; as a result, the injection into the anterior chamber of a standard amount of a stock solution of methylene blue in the manner recommended did not always stain the superficial fibers of the thicker corneas.

The disadvantages of the supravital method have been outlined previously (Rodger[13]), although inconsistency was not one of them. The general tissue staining, which often confuses the supravital-staining picture, can be completely eradicated if the excised corneas are placed in warm buffered saline, in the manner first recommended by Schabadasch.[14] The slight distortion of the nerve fibers, which also occurs, did not matter, as we were not interested in the characteristics of the fibers. We sought only to determine whether or not degeneration was complete.

The cornea on the side of operation was compared with that on the intact side, the pair being stained simultaneously with the same solution. All the photomicrographs were taken from fresh viable corneas, before fixation, as even in the most practiced hands fixed specimens are unreliable (Rodger[15]). The 12-o'clock meridian on each cornea was marked by an incision prior to staining, and the distribution of the nerve bundles, after charting, could then be related to the responses previously obtained from these same areas.

Postmortem Confirmation of Operative Procedures.—Although the technique permits the procedure to be carried out under direct vision (with difficulty in case of the intradural sections), the operative appearance is frequently deceptive. Furthermore, naked-eye examination of the nerve trunks at autopsy can be equally misleading. The divided nerve is held together by a plug of clotted blood, the removal of which may snap any uncut nerve fibers still remaining. The opposite state of affairs also exists. When a few peripheral nerve fibers apparently remained, histological examination on several occasions showed them to consist only of fibrous tissue. Postmortem histological examinations are, therefore, essential. The Marchi technique was the method of choice. The distal ends not only of the cranial nerve in question but also of its immediate neighbors were examined, so that, in addition to determining the success or failure of the section, we might also ascertain the presence of accidental damage to other nerve trunks.

12. Weddell, G., and Zander, E.: J. Anat. **84**:168, 1950.
13. Rodger, F. C.: Tr. Ophth. Soc. U. Kingdom **71**:687, 1951.
14. Schabadasch, A.: Ztschr. Zellforsch. u. mikr. Anat. **10**:221, 1930.
15. Rodger, F. C.: Brit. J. Ophth. **34**:107, 1950.

Early in these investigations, it was observed that dilatation of the pupil frequently followed the operation, although the third nerve had not been sectioned. In such cases it was thought that the nerve had been cut accidentally. On histological examination, however, this was found not to be so. It was assumed, therefore, that pupillary dilatation of this nature must be due to functional derangement, perhaps as a result of the pressure of extravasated blood. Later, being prepared for this, we noted that the pupil invariably returned to its normal diameter and regained its normal activity (the third nerve being uncut) in from three to seven days after operation, thus confirming the functional nature of this sign.

Summary of the Operations.—The various neurectomies, with relevant data, are summarized in the following tabulation.

	No. of Cats
Complete division of ophthalmic branch distal to cavernous sinus	4
Partial division of ophthalmic branch distal to cavernous sinus	4
Complete division of ophthalmic branch proximal to cavernous sinus	2
Complete division of maxillary branch about 3 mm. from Gasserian ganglion	2
Complete division of oculomotor nerve proximal to cavernous sinus	2
Complete division of superior cervical sympathetic chain and removal of superior cervical sympathetic ganglion	2
Anesthetic deaths	2
Postoperative death, lobar pneumonia	1
Postoperative death, intracranial hemorrhage	2
Total	21

RESULTS

Appearance of the Degenerating Corneal Nerve Fibers.—One would expect the distal parts of the ophthalmic nerve fibers lying in the cornea to degenerate fairly rapidly after intracranial section. The earliest postoperative period at which I was able to observe these changes was two days (Cl. 8). At this time the smaller nerve fibers, although irregular and varicose in appearance, were otherwise intact. The Schwann cells, moreover, revealed few signs of the active proliferation so characteristic of them later. As I have already mentioned that distortion of the nerve fibers in vital staining is a distinct possibility, fragmentation, obviously, must be the principal criterion as to whether or not the nerve section has been successful. In total ophthalmic neurectomies, this state of affairs was always found by the sixth day (Fig. 1). The characteristic appearance at this stage was one of columns of fragmented remnants radiating in "palisade" fashion from the limbus, while the re-formation of the Schwann element had only just started (Fig. 2).

The degeneration of the corneal nerve fibers coincided with reactive changes in the stromal cells. In all preparations, it was found that the processes of these cells became irregularly varicose (Fig. 3*A*). In addition, in many places the processes were withdrawn, in the manner of iris chromatophores, the cells breaking away from the syncytium and their appearance thereafter corresponding to that of the macrophages found around the degenerating fibers (Fig. 3*B* and *C*). No great evidence of leucocyte activity, such as occurs in a corneal graft, existed, and it was assumed that the macrophages, which were abundant, were derived from the local tissues in the manner described. They might, of course, have originated from the Schwann sheaths, rather than from the corneal corpuscles.

Coinciding with these changes, the Schwann cells soon exhibited a conspicuous proliferation. They formed solid tubes of protoplasmic tissue, consisting of parallel

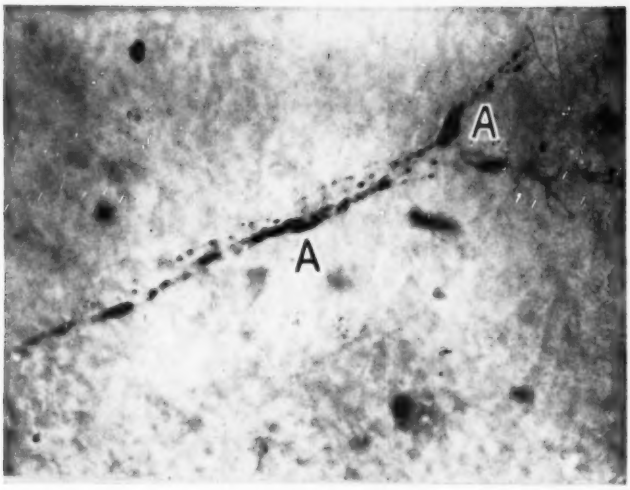

Fig. 1.—Fragmentation of corneal nerve fiber six days after division of the ophthalmic nerve. Mitoses of Schwann nuclei can be seen at *A*. Methylene blue; × 550.

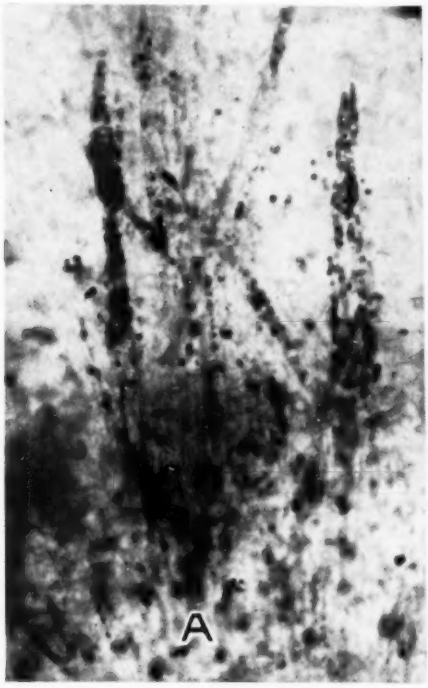

Fig. 2.—Appearance of corneal nerve fibers at the periphery eight days after division of the ophthalmic nerve. The Schwann nuclei have started to proliferate; scavenger cells have removed most of the degenerating nerve fibers centrally, and only here, at the periphery, may columns of nerve remnants be seen, radiating in characteristic "palisade" fashion from the limbus (*A*). Methylene blue; × 200.

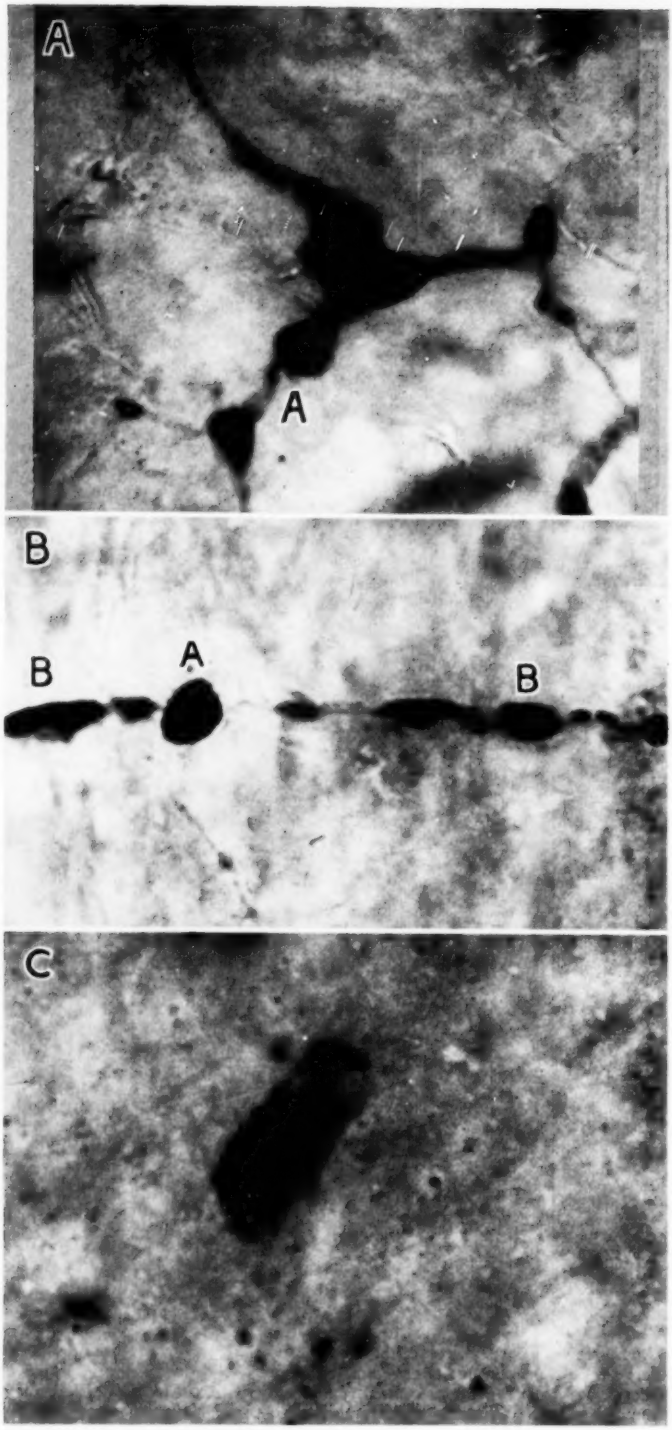

Fig. 3.—*A*, reaction of the corneal corpuscles to nerve fiber degeneration. The irregular thickening of the processes and the clumping of the cytoplasm around the nuclei are well seen. The cell, at A, appears to be breaking free. This is a probable origin of the many macrophages found around the degenerating fibers. Methylene blue; × 1,200.

B, single degenerating nerve fiber. At A is a macrophage; at B are Schwann nuclei. Methylene blue; × 1,000.

C, macrophage filled with chromatin fragments. No nerve fibers remain in this region of the cornea. Methylene blue; × 1,300.

rows of cells and fibers, which extended along the course taken originally by the nerve fibers (Fig. 4). Thus, the characteristic pathways were maintained for the direction of the regenerating nerves. At the outset, the continuity of the Schwann cell element was frequently broken; the reparative processes, as a result, started simultaneously wherever Schwann nuclei existed (Fig. 5 *A*).

In the deep multifiber bundles, these Schwann tubes are thick, but as they keep on dividing, they become thinner and thinner until in the end single sheaths alone remain (Fig. 5 *B*). These solitary single nerve sheaths in the corneas on the side of operation could be mistaken for nerve fibers. The entire Schwann system,

Fig. 4.—Proliferation of the Schwann tube 10 days after division of the ophthalmic nerve. Note the parallel rows of the cells and their processes and the characteristic radiate branching. Some fragments of nerve fibers still remain within the tube. Methylene blue; × 550.

however, adopted a much less sinuous course than in the original, intact plexuses; furthermore, the absence of beading (Fig. 5 *C*), so characteristic when nerve fibers are present, was a striking feature, leaving little doubt that the single sheaths in question were empty.

Experimental Results in Detail (Table).—Group 1 (A and B): Complete Division of Ophthalmic Nerve: The nerve was cut extradurally distal to the cavernous sinus in four cats and proximal in two cats. In all six animals there was complete degeneration of the nerve fibers in the cornea. That is, all the nerve fibers had fragmented, and, depending on the duration of the experiment, the

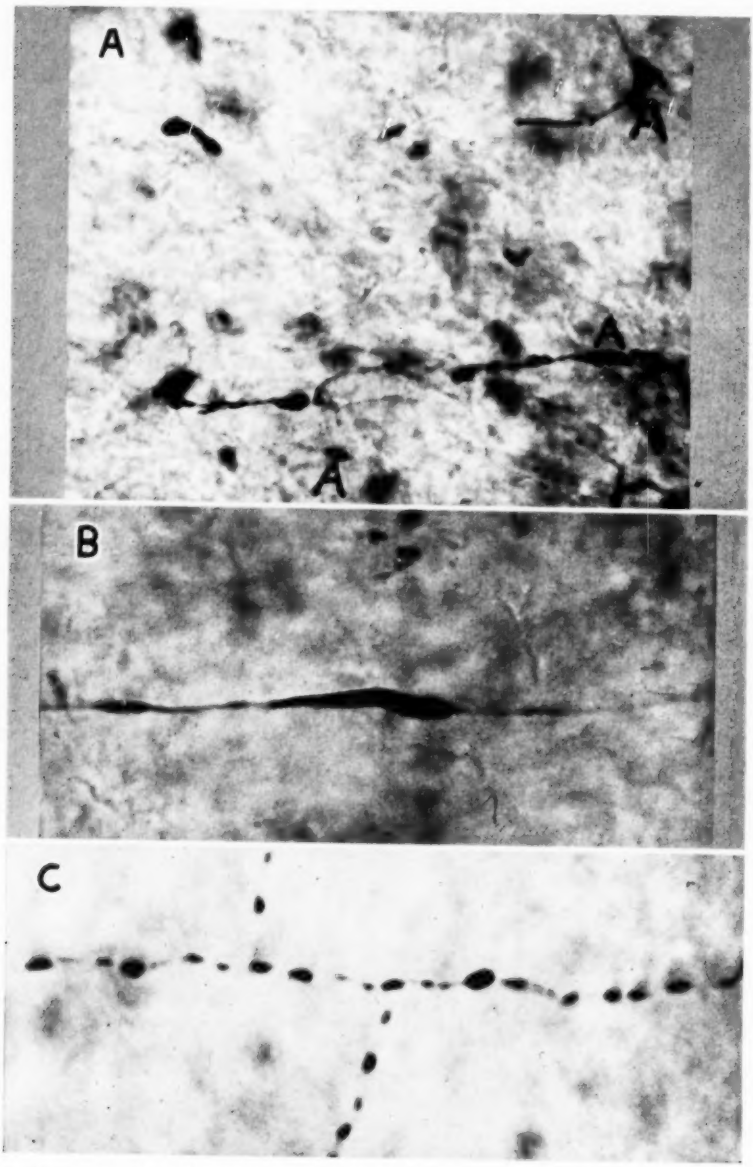

Fig. 5.—*A*, central region of the cornea eight days after division of the ophthalmic nerve. The nerve fibers have almost completely disappeared. At A are typical Schwann nuclei; from these remnants protoplasmic tubes will rapidly develop to form a scaffolding for the regenerating nerve fibers. Methylene blue; × 200.

B, Schwann sheath covering a single corneal nerve fiber. The absence of beading suggests that the sheath is empty. This picture was taken seven days after complete division of the ophthalmic nerve. Methylene blue; × 550.

C, single nerve fiber and its collateral branches in the healthy cornea, included for comparison with *B*, showing the presence of beading. Methylene blue; × 600.

fragments were either partially or wholly phagocytosed; in addition the Schwann nuclei showed many mitotic figures (Fig. 6), re-forming to varying extents the structural neurilemmal pathway of the future nerve plexuses; finally, the characteristic reaction, previously described, of the stromal cells could be seen

In four of the six cats there were central opacities of the cornea. In the other two cats the corneas were clear. Sensibility in all six was nil; the ocular movements

Effect on Cornea of Various Neurectomies

Serial No.	Experiment Terminated, Day	Histological Appearance	Corneal Sensibility
Group 1A: Complete Division of Ophthalmic Branch of Fifth Nerve Distal to Cavernous Sinus			
Cl. 4	7th	Total degeneration of all corneal nerve fibers	Nil
Cl. 8	2d	Cat found dying on 2d morning after operation; large intracranial haemorrhage revealed post mortem	.....
Cl. 11	8th	Total degeneration of all corneal nerve fibers	Nil
Cl. 12	—	Postoperative death from lobar pneumonia	.....
Cl. 13	21st	Total degeneration of all corneal nerve fibers	Nil
Cl. 15	..	Anesthetic death	.....
Cl. 16	6th	Total degeneration of all corneal nerve fibers	Nil
Group 1B: Complete Division of Ophthalmic Branch of Fifth Nerve Proximal to Cavernous Sinus			
Cl. 18	7th	Total degeneration of all corneal nerve fibers	Nil
Cl. 21	10th	Total degeneration of all corneal nerve fibers	Nil
Group 2: Partial Division of Ophthalmic Branch of Fifth Nerve Distal to Cavernous Sinus			
Cl. 3	13th	Outer fourth cut: Degenerating nerve fibers here and there in lower half-cornea	Type A throughout
Cl. 5	14th	Outer five-sixths cut: One large multifiber nerve bundle intact in lower medial quadrant; from it a few fine itinerant nerve fibers spread over the cornea	Type A response in small area (lower medial sector); elsewhere Type B response, fading in places to no sensibility
Cl. 6	8th	Outer half cut: 6 intact nerve bundles counted, 5 of them nasally; signs of degeneration in all four quadrants; many fine intact nerve fibers passing apically toward central opacity	Type B response throughout, except for small region near caruncle, where Type A was present
Cl. 10	9th	Outer two-thirds cut: 4-5 multifiber nerve bundles in upper nasal quadrant; in lower temporal quadrant only degenerating nerve fibers	Narrow upper nasal strip gave Type A response; outer third, no sensibility; in broad central region Type B response very marked
Group 3: Complete Division of Maxillary Branch of Fifth Nerve 2 Mm. from Gasserian Ganglion			
Cl. 7	—	Anesthetic death	.....
Cl. 9	10th	No sign of nerve fiber degeneration in cornea	Type A response throughout
Cl. 14	7th	No sign of nerve fiber degeneration in cornea	Type A response throughout
Group 4: Complete Intradural Division of Oculomotor Nerve Proximal to Cavernous Sinus			
Cl. 17	—	Postoperative death: Large subdural hemorrhage and temporal lobe lacerations revealed post mortem	.....
Cl. 19	7th	No sign of nerve fiber degeneration in cornea	Type A response throughout
Cl. 20	7th	No sign of nerve fiber degeneration in cornea	Type A response throughout
Group 5: Complete Division of Cervical Sympathetic Chain and Removal of Superior Cervical Sympathetic Ganglion			
Cl. 1	14th	No sign of nerve fiber degeneration in cornea	Type A response throughout
Cl. 2	16th	No sign of nerve fiber degeneration in cornea	Type A response throughout

were full, and the pupils were equal, reacting directly, consensually, and in accommodation.

Group 2: Partial Division of the Ophthalmic Nerve: In four cats partial division of the ophthalmic nerve was performed. Depending on the extent of the section, a few intact bundles were observed grouped together in the same quadrant. Degenerating nerve fibers were present in the other quadrants. In the latter, however, the quadrant or quadrants adjacent to the healthy fibers were seen to receive from

that source some fine intact fibers (Fig. 7*A*). There was in all four animals, however, at least one quadrant which had no intact fibers in it.

The response in an area roughly corresponding to the quadrant with intact nerve bundles was that designated as Type A (Fig. 7*B*). The response in those quadrants in which a few intact fibers alone remained (Fig. 7*C*) was that designated as Type B. The areas giving this response were noticeably hypesthetic. Sensibility in the remaining quadrants, those in which no intact nerve fibers could be found, was nil.

In three of these four cats there was a small apical opacity. The pupils in all four were equal and reacted. Ocular movements were full.

Group 3: Complete Division of the Maxillary Nerve: There was no sign of nerve fiber degeneration. The corneas were clear, and the reaction to tactile stimulation was of Type A throughout—in short, sensibility was unaffected. Ocular movements were full, and the pupillary reactions were normal.

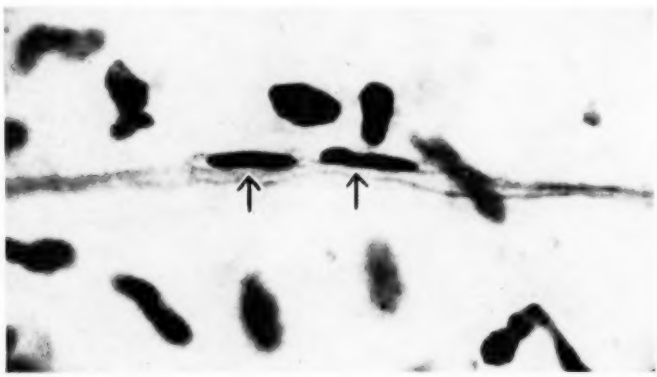

Fig. 6.—Two Schwann nuclei and an empty neurilemmal tube in a small portion of cornea stained with silver. Silver nitrate; × 440.

Group 4: Complete Division of the Oculomotor Nerve: In neither of the two successful experiments of this type was any degeneration of the corneal nerve fibers seen. Sensibility was unaffected, and the corneas were clear. The pupils on the side of operation were dilated and fixed, and the eyes deviated outward.

Group 5: Complete Division of the Cervical Sympathetic Chain and Removal of the Superior Cervical Ganglion: No evidence of corneal nerve fiber degeneration was found in either animal. The corneas were clear; sensibility was unaffected; the pupils were equal and reacted normally; the ocular movements were full.

COMMENT

Source of the Corneal Nerve Fibers.—The neurosurgical procedures executed gave reasonably satisfactory answers to the questions originally asked.

In 1948 I performed cervical sympathectomies (distal to the superior cervical ganglion) in three rabbits and learned at that time that no degeneration resulted in the corneal nerve plexuses. This result was not published, as it was well known

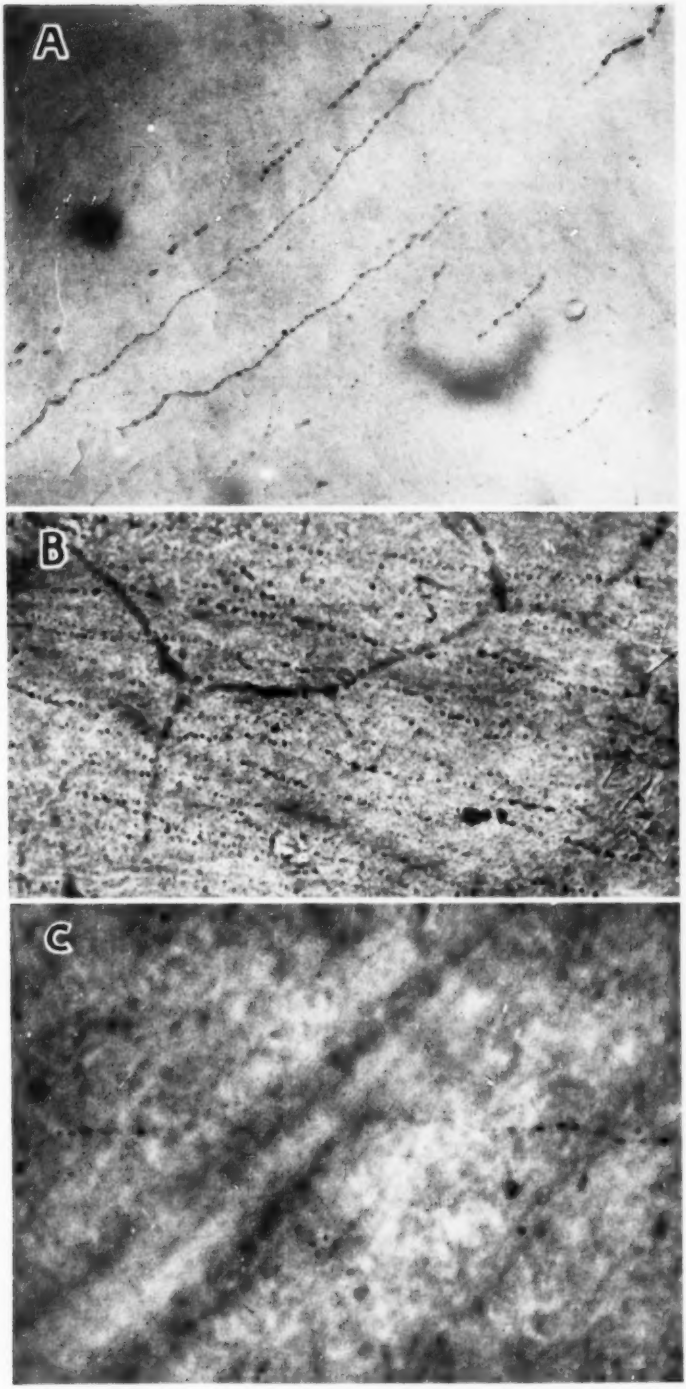

Fig. 7.—*A*, partial division of the ophthalmic nerve. Coursing through a quadrant of degenerating nerve fibers is a single fine nerve fiber, whose continuity with a healthy nerve bundle in an adjacent quadrant could be traced. This is a picture of the surface receptors underlying the Type B response (CI. 6). Methylene blue; × 200.

B, surface receptors underlying the Type A response in normal, healthy cornea. Methylene blue; × 150.

C, partial division of the ophthalmic nerve, as in Figure 7 *A* (CI 5). The cornea in this animal had lost a great deal of its translucency. Type B response was marked. Methylene blue; × 200.

to the older histologists. Our present investigations in the cat (Cl. 1 and 2) and those published recently by Zander and Weddell [16] on the results of performing this operation in five rabbits encourage us to feel that there should be no reason to question again this established belief. In 1935, Boeke [5] described two types of cor-

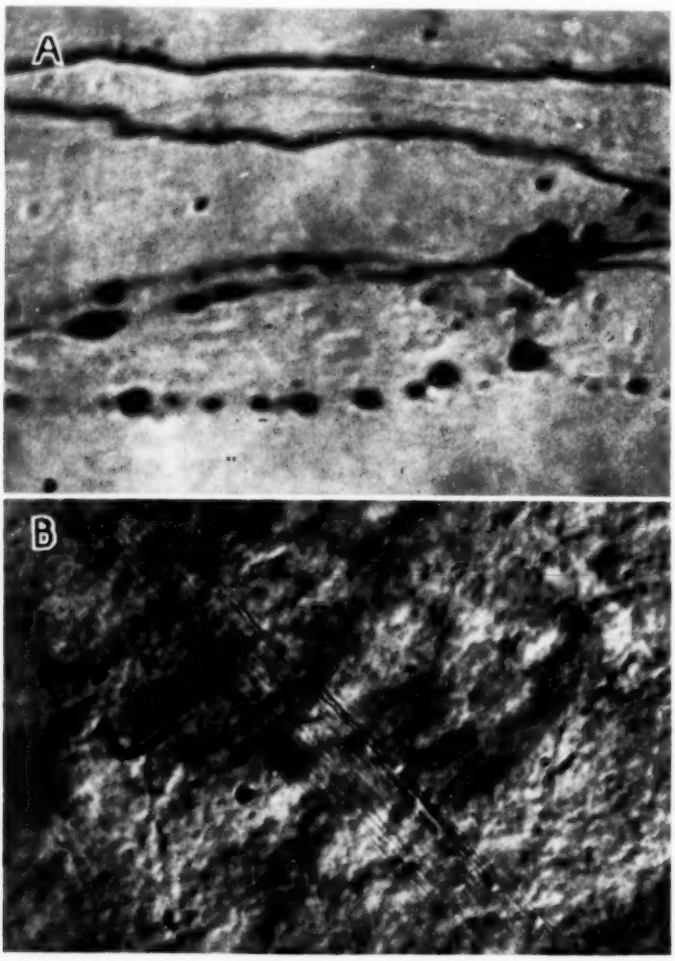

Fig. 8.—*A*, two types of nerve fibers found in the vitally stained cornea—one beaded; the other not. The nonbeaded type is myelinated, the myelin presumably protecting the nerve fiber within. My view is that beading is an artifact.[17] Methylene blue; × 1,500.

B, myelinated nerve fiber advancing deep into the corneal stroma. The dark myelin is interrupted at the nodes of Ranvier. Phase contrast; × 750.

neal nerve fibers, anatomically distinct, one of which he considered, on morphological grounds, to be sympathetic, the other sensory. This observation was con-

16. Zander, E., and Weddell, G.: Brit. J. Ophth. **35**:61, 1951.

firmed (Rodger [15]), pictures being published of the two types of fibers in question (Fig. 8*A*). Later (Rodger [17]) evidence was supplied which was strongly suggestive that the less frequently observed, coarser type of fiber was merely one which had retained its myelin sheath and that there is no other difference between the two types (Fig. 8*B*). Although it is the general opinion that the myelin sheaths disappear a millimeter or two beyond the limbus, these observations [17] were made by using negative-phase and polarizing microscopy and would appear conclusive. Ernyei,[18] staining the corneas of dogs, cats, pigs, sheep, horses, oxen, and rabbits with Kiss's osmic-acid method, also noted that some of the nerves kept their sheaths for some distance into the corneal stroma. Boeke's argument in favor of the occasional pres-

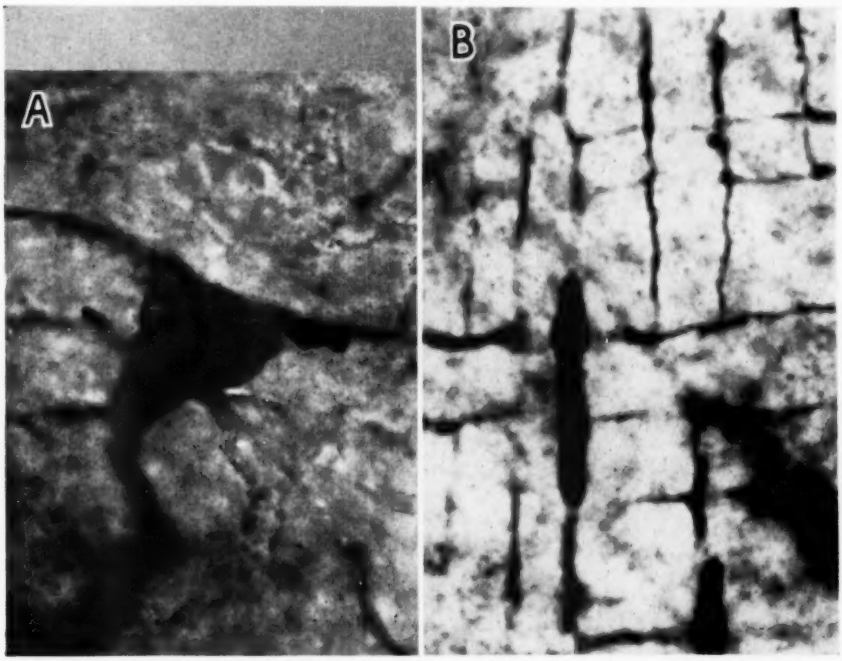

Fig. 9.—*A*, curiously shaped stromal cell, not unlike a nerve ganglion cell. Methylene blue; × 770.

B, stromal cells (corneal corpuscles) and their processes. The peculiar "lattice-work" arrangement is characteristic. For short intervals the nerve fibers follow the course of the processes. Silver nitrate; × 250.

ence of sympathetic fibers on the ground of a morphological difference between the two, appears, then, to be false.

Zander and Weddell [8] claimed to have occasionally seen ganglion cells in the cornea. Ernyei, on the other hand, who examined many hundreds of corneas, stated that he had never seen such structures. The photomicrograph of such a ganglion

17. Rodger, F. C.: J. Physiol. **115**:67P, 1951.

18. Ernyei, I.: von Graefes Arch. Ophth. **132**:140, 1934.

cell, which Zander and Weddell reproduced in their paper, is not very convincing. It bears a close resemblance, in fact, to a partially detached corneal fibroblast (Fig. 9*A*).

While one can be fairly dogmatic in stating that there are no sympathetic nerve fibers or cells in the cornea, it is less easy to prove or disprove the presence of parasympathetic fibers. Nageotte and Guyon [8] claimed that, in addition to sensory fibers from the ophthalmic nerve, there are many parasympathetic fibers from the oculomotor nerve, the ciliary nerves supplying the cornea being a mixture of the two. They called these fibers the "interstitial" nerves of the cornea and described them as being long fibers of minute diameter, unmyelinated, and in their course closely following the interlamellar cement. At this point, one is tempted to conclude that Nageotte and Guyon have made the mistake of confusing the fine cement-coated

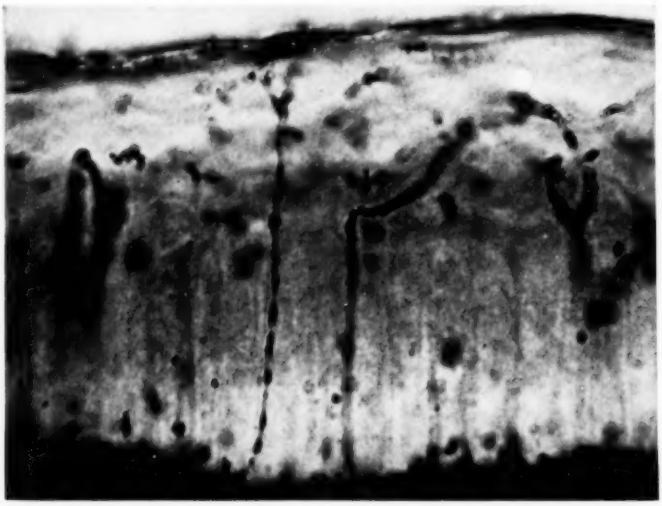

Fig. 10.—Free corneal ending within the epithelium. The fragmentation is an artifact, due to imperfect impregnation. Gold chloride; × 650.

processes of the stromal syncytial cells with nerve fibers, especially since with modern histological methods the two are seen frequently to follow a similar course (Fig. 9*B*). The techniques they used, moreover, were the rather nonspecific ones of gold and silver impregnation, both metals being deposited on the cement, as well as the nerve fiber. The main argument of the French school, however, rests on the results of two intradural oculomotor neurectomies which they performed on dogs. These sections led to signs of degeneration in the "interstitial" fibers. The results could readily be explained, of course, on the ground that gold and silver impregnations are notably uncertain (Fig. 10); alternatively, it may be said that damage to the adjacent sensory fibers of the fifth nerve was responsible. Since the continuity of the various cranial nerves in question was not investigated post mortem, the latter theory is a possibility. Whatever the explanation may be, the present experiments have not confirmed this finding (Cf. 19 and 20).

Several other authors, nevertheless, have supplied indirect evidence favoring the belief that parasympathetic fibers exist in the cornea.

Knapp [3] reported a case of deep corneal opacification following extirpation of the lacrimal gland—as distinct from the more usual filiform epithelial lesion—and suggested that the operation had damaged parasympathetic fibers passing through the gland to supply the cornea. Other, more obvious explanations might be given, however; and Knapp's hypothesis should remain no more than an interesting suggestion. Interference with the sensory innervation, or with the blood supply, appears just as likely to be the causative factor.

Behr [2] and Marchesani [7] were others of the opinion that autonomic efferent fibers pass in the ophthalmic division to supply the cornea. Their evidence was equivocal. They concluded that neuroparalytic keratitis associated with lesions of the Gasserian ganglion could only result from damage to such nerves. Marchesani believes that the fibers responsible are parasympathetic ones, which attach themselves to the ophthalmic nerve within or distal to the cavernous sinus. In the present studies, however, no appreciable variation in the state of degeneration existed in sections proximal and distal to the sinus (e. g., CI. 4 and 18). Behr's belief that there is a parasympathetic outflow through the fifth cranial nerve root has never been substantiated, and is unlikely.

Although the ophthalmic nerve may, and probably does, receive autonomic fibers from other sources as it passes toward the eye, it seems certain (CI. 18, 19, 20, and 21) that none of these ancillary fibers enters the cornea. Further, the absence of any degeneration of the corneal nerve fibers after section of the maxillary division (CI. 9 and 14) encourages one to believe that the suggestion of Jefferson [4] that this division supplies the lower half of the cornea is, at least in the case of the cat, untrue.

It has been demonstrated conclusively by various authors that the fundamental anatomical unit of sensation in the cornea is a single nerve fiber which terminates as a plexiform continuum and from the surface of which free endings grow out between the cells of the epithelium. There appears to be strong evidence in the present studies that the only source of these fibers is the ophthalmic division of the trigeminal nerve.

Nature of Corneal Sensation.—It has already been indicated in this paper how the reactions of the experimental animals were elicted, and what was the basis for their classification as Type A and Type B responses. From a comparison with the reactions obtained from the corresponding regions of the cornea on the intact side, it became obvious that some such gradation in sensibility existed, the Type A response being very painful, whereas the Type B response was much reduced in intensity.

In the four cats in which partial section of the ophthalmic nerve was performed (CI. 3, 5, 6, and 10), the reactions obtained from the partially denervated corneas were correlated with the underlying nerve pattern. As a result, it was found that sensation in those regions in which only one or two fibers and their endings remained gave every evidence of being hypoaesthetic, the Type B response. Here, then, presumably, is a possible structural basis for hypesthesia. At least, it can be said that when the average number of pain endings is diminished, the response to a stimulus painful in the corresponding region of the eye on the intact side is no longer so, although it is apparently felt.

At first sight, the responses elicted from the partially denervated corneas appear to correspond with the clinical observations of Trotter and Davies.[19] These authors described how, after section of a cutaneous nerve, the area of complete sensory loss was surrounded by a zone of hypesthesia the exact qualities of sensation in which were, they admitted, somewhat difficult to interpret. The pattern of nerve distribution found in the four-cat corneas in question would explain such an observation adequately.

It is not clear, however, why intact corneal nerve fibers and their endings, when stimulated painfully, do not respond in the specific manner, as it is generally considered that cutaneous pain sensation is punctate (not, of course, that each spot contains an ending derived from a separate neurone). Although the anatomical unit of corneal sensation is the entire distribution of one nerve fiber, one does not obtain the sensation of pain only on stimulating the complete unit. A stimulus at any part of it appears to set up activity in the whole (Tower [20]). In short, the punctate nature of cutaneous sensation in the cornea is even more evident than in the skin. In view of this, it would seem reasonable to assume that here, as in the skin, the physiological unit of pain is the free intraepithelial ending, while two-point discrimination and localization of painful stimuli depend on the overlapping of adjacent nerve plexuses. All the more reason, then, to explain the absence of a Type A response in a Type B area.

In the intact cornea, of course, the Type A response occurs in a region where spatial summation is impossible to eliminate, a physiological factor the absence of which, when the number of endings is reduced, as by operation, may be responsible for the phenomenon called hypesthesia. This explanation would appear to be a likely one. In the light of it, the Type B response, which presumably resulted from stimulation of the few isolated free endings present, must be considered one fundamentally of pain, although pain apparently of an intensity so slight that it no longer hurts the animal. Boberg-Ans [21] has shown that the end of a nylon thread covers 4 to 10 nerve endings. A strand of lint probably covers twice this number of endings. Our estimate in the case of the cat CI.5, which gave a Type B response, is that we never stimulated more than two to four nerve endings at any one time in the Type B area.

This leads me to underline one of the greatest difficulties in discussing the subjective aspects of pain and touch, namely, that, such a wide range of qualities having been listed under these heads, there appears to be a considerable overlap in meaning. This ambiguity is well illustrated, for example, in the work of Boring.[22]

The initial sensation that ensues upon minimal degrees of pinprick has often been described as light touch (Woollard, Weddell, and Harpman [23]; Heinbecker, Bishop, and O'Leary [24]). This has led to the suggestion that pain endings serve both a tactile and a pain function. In the case of the cornea such a suggestion has crept in and out of the literature, although it is difficult to find any justification for

19. Trotter, W., and Davies, H. M.: J. Physiol. **38**:134, 1909.
20. Tower, S. S.: A. Res. Nerv. & Ment. Dis. Proc. **15**:167, 1935.
21. Boberg-Ans, J.: Corneal Sensitivity, Thesis, Copenhagen, 1952.
22. Boring, E. G.: Quart. J. Exper. Physiol. **10**:1, 1916.
23. Woollard, H. H.; Weddell, G., and Harpman, J. A.: J. Anat. **74**:413, 1940.
24. Heinbecker, P.; Bishop, G. H., and O'Leary, J.: Arch. Neurol. & Psychiat. **31**:34, 1934.

it. Tower [11] recorded single impulses, or short bursts, on touching cat corneal epithelium, whereas deeper deformation of its surface gave rise to higher frequency discharges. Thus, apparently, two sensations existed—the first, she stated, indicative of a tactile quality, the second of pain. Until, however, Tower eliminates other types of receptors in the sclera and choroid which are bound to be stimulated on deforming the cornea, there is no real evidence that the corneal nerve fibers subserve both touch and pain sense. It is more difficult to disturb the even tenor of Bishop's [25] experiments. He claimed that the same endings in his own skin, when stimulated electrically, originated a series of different sensations, depending on the frequency and intensity of the stimulus, sensations which he interpreted as varying from light touch to acute pain.

In the light of Bishop's findings, it might be argued that in the present experiments the Type B response did not result from a diminished sensation of pain, but because the true nature of the free corneal endings, exposed because the number of endings was reduced to a minimum, is one of touch. This presupposes the rather rash assumption that, by summation in the profusely innervated intact cornea, a change in the perceptual quality of "touch" will result, so that a tactile stimulus becomes painful.

In all these arguments the law of specific nerve energies is placed in jeopardy, for, as the specialized endings described by Dogiel and Attias [27] are now known to be artifacts (Rodger,[28] Zander and Weddell,[8] and others), there is only one type of receptor in the cornea for the two modalities—the free ending. It is well known that the mass of evidence apparently supports the law in question (Wollard, Weddell, and Harpman [23]; Cattell and Hoagland,[29] and Adrian [30]). The sum of the evidence, however, is that pain is not aroused by overstimulation of tactile endings. Is one justified in concluding on these premises that the converse is also true, i. e., that touch cannot be aroused by understimulation of pain endings? One presumes that one is.

It is interesting to note, nevertheless, that there is surgical evidence in favor of the belief that the corneal endings are sensible to touch as well as to pain. Rowbotham,[9] by cutting the descending root of the fifth cranial nerve in the medulla for relief of trigeminal neuralgia (the Sjoqvist operation), was probably the first to make the extremely important observation in man that, although no pain was felt in the cornea, stimulation elicited a sensation described by his subjects as one of "touch." This operation was repeated and confirmed by Grant, Groff and Lewy,[10] and by Olivecrona.[31] Thus, here is apparently a state of affairs eminently satisfactory to the anatomist, for it reflects exactly the pathways taken by the fibers subserving touch and pain in the spinal segments. The bifurcation of the pontine fibers of the trigeminus becomes intelligible in its light. There is no doubt that Tower was greatly influenced by these observations. It could, of course, also be

25. Bishop, G. H.: J. Neurophysiol. **6**:361, 1943; ibid. **7**:71 and 185, 1944; ibid. **12**:51, 1949.
26. Dogiel, A. S.: Anat. Anz. **5**:483, 1890.
27. Attias, G.: von Graefes Arch. Ophth. **83**:207, 1912.
28. Rodger, footnotes 15 and 13.
29. Cattell, M., and Hoagland, H.: J. Physiol. **72**:392, 1931.
30. Adrian, E. D.: The Mechanism of Nervous Action: Electrical Studies of the Neurone, Philadelphia, University of Pennsylvania Press, 1932.
31. Olivecrona, H.: Arch. Neurol. & Psychiat. **47**:544, 1942.

explained on the grounds that by diminishing the number of pain endings by half, a hypesthesia was produced, the unfamiliar quality of which was interpreted as "touch" by the patients.

If the possibility be accepted that the trigeminal nerve consists of pain and touch fibers which separate out within the central nervous system, passing to different nuclei, the case can only be proved if and when the pontine fibers are cut, and touch is thereby eliminated. In the present experiments, however, there are no signs that such a congruency exists in the ophthalmic division. The results suggest a rough topographical separation at this level, but, on analysis, no more than that. It is most unlikely, therefore, that in the four cats in which the Type B response was elicted, the "pain" fibers alone had been cut and the "touch" fibers spared. That would be too much of a coincidence. Until the ascending fibers have been cut, therefore, the evidence provided by the Sjöqvist operation must be viewed with great care.

Very recently, Cogan and Ginsberg [32] described a case of lateral medullary thrombosis in which the cornea was completely anesthetic, and in the face loss of pain, but only slight reduction in tactile sensation, occurred. From this it may be inferred that the corneal sensation is represented in the brain stem along with the facial sensation of pain, and not with that of touch. This is an important finding, strongly supporting the present view that the sensation described as "touch" which resulted from the Sjöqvist operation was merely a manifestation of hypesthesia.

In the circumstances, it would seem that the most one can assume at this stage is that the intensity of pain elicted on stimulation of one nerve ending is different from that on stimulation of several. The pain sense would appear to increase or decrease in direct proportion to the number of endings. Babel and Campos [33] have shown that the terminal nerve nets of the cornea seldom re-form completely in corneal grafts, and sensation in such grafts, it is well known by clinicians, is always blunted. In fact, Babel and Campos described the quality as "tactile." Egorov [34] noted the opposite state of affairs. After keratectomy, hyperesthesia occurred at a time when regeneration of nerve fibers was excessive. Not until the nerve fibers became reduced to within a normal extent did this hyperesthesia diminish.

In the light of these arguments, it may well be that the varying sensibility to pain found in different persons, and generally attributed to psychological factors, may, after all, be largely determined peripherally. Certainly, it leaves one with many interesting propositions.

SUMMARY

Complete division of the following nerves in cats was performed intracranially: the oculomotor, the maxillary, and the ophthalmic—in the case of the last nerve, both proximal and distal to the cavernous sinus. In addition, division and removal of the superior cervical ganglion and chain were done, and in four cats partial division of the ophthalmic branch alone. The animals subsequently were killed at intervals varying from 6 to 21 days. Before death, however, a record was made

32. Cogan, D. G., and Ginsberg, J.: A. M. A. Arch. Ophth. **47**:273, 1952.

33. Babel, J., and Campos, R.: Ophthalmologica **111**:140, 1946.

34. Egorov, I.: Vestnik oftal. **16**:3, 1940.

of the reactions of the animals on stimulating the corneal quadrants on the side of operation with lint. The reactions, specified as Type A (pain) and Type B (reduced sensitivity), were then correlated with the nerve pattern after death.

The method of vitally staining the corneal nerve fibers, and the signs indicative of their partial and complete degeneration, are described, and some fallacies are discussed. The success of the operations was confirmed post mortem, with the Marchi technique.

It is concluded that the nerve fibers supplying the cornea of the cat originate entirely from the ophthalmic division of the fifth cranial nerve. No autonomic nerve fiber that might add itself to this nerve in the region of the cavernous sinus passes beyond the limbus, nor was any nerve ganglion cell ever found within the cornea.

In those corneas in which the nerve fibers had only partially degenerated, the reaction of the animal to the stimulus was in certain regions greatly reduced. The structural basis of this hypesthesia was found to be a diminution in the number of existing nerve endings. For this reason, it is considered that the two responses —the painful and the reduced—were but two aspects of the one sensory experience.

It is considered that these findings provide evidence suggesting the possible structural basis of hypesthesia, and that the free intraepithelial endings in the cornea are receptors only for pain.

Dr. Kathleen Bell administered the anesthetic, and Dr. A. R. Kirby assisted me in the operations.

UNIPOLAR ANODAL ELECTROLYTIC LESIONS IN THE BRAIN OF MAN AND CAT

Report of Five Human Cases with Electrically Produced Bulbar or Mesencephalic Tractotomies

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AND
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NEAR THE end of the last century, Golsinger (1895), cited by Roussy,[1] presented the brains of six dogs with isolated lesions produced by unipolar electrolysis with a current of 20 to 40 ma. Sellier and Verger[2] (1898) made their small lesions deep in the brains of three dogs with a bipolar electrode passing a current of 9 to 15 ma. for 7 to 10 minutes. Horsley and Clarke[3] (1908) studied carefully some of the physical principles involved in such a use of electrodes and demonstrated that much less gas was evolved, and in a less explosive manner, at the anode than at the cathode; hence their anodal lesions were more constant in size than those produced at a cathode or with a bipolar electrode. After many observations, they ventured the statement that for a unit of time, "e. g., one minute, there will result about 1 mm. breadth of destruction for each 1 ma. of current employed." They found this to be true up to about 5 ma. Although they stated that this value is only approximate, the rule of thumb they gave appears to have guided neurophysiologists for decades.

METHODS AND RESULTS

1. *Human Brain Stem.*—In the course of the extensive studies of Ranson, Magoun, and their collaborators, circumscribed lesions were made deep in the central nervous system of animals. They noted that it was particularly difficult to produce a large lesion by use of more current for a longer period, and to this end they found it necessary to reposition the electrode and reapply the current.[4] This limitation seemed to be a valuable safety factor.

On the basis of their wide experience we decided to try the same technique in making lesions in the brain stem of man, observing the following factors: Since the pain fibers from the cervical and upper thoracic segments probably lie at a depth of 3 to 6.5 mm. in the medullary bulb, we hoped to avoid unnecessary damage to the surface of the medulla and to eliminate the need of dividing any pial vessels. In addition, we hoped that the use of a unipolar electrode

1. Roussy, G.: La couche optique, Thesis No. 165, Paris, G. Steinheil, 1907.

2. Sellier, J., and Verger, H.: Recherches expérimentales sur la physiologie de la couche optique, Arch. physiol. norm et path. **10**:706-713, 1898.

3. Horsley, V., and Clarke, R. H.: Structure and Function of the Cerebellum Examined by a New Method, Brain **31**:45-124, 1908.

4. Magoun, H. W.: Personal communication to the authors.

transmitting direct current for making the lesion would decrease the likelihood of hemorrhage from within the central neuraxis by coagulating any blood vessels within its range. In attempting mesencephalic tractotomy according to Walker's technique, we have divided arteries of significant size within the midbrain, a complication we have not encountered in incising the bulb or cord. The arterial blood flow emerging from within the incision made by a knife blade has been difficult to arrest without major damage. Consequently, we have made lesions in the medulla electrically in four patients and in the mesencephalon in one patient. Each was awake during the time of passage of the current, and in four of the five patients there was no discomfort or untoward behavior.

Nichrome (nicochrome) electrodes were provided us by Professor Magoun. These consisted of No. 20-guage wire covered with insulating varnish except for 1 mm. at the bare tip. This electrode was made the anode, and the other electrode, at which more gas forms when the two are placed in saline, was attached to a large metal plate against the patient's skin. Current was delivered by the Goodwin-Stein lesion maker, which provides a steady source of direct current, whose value is constantly obtainable from a milliammeter in the circuit. This current was maintained at 3 ma.; only the duration was varied.

In patient P. S. the electrode was inserted into the medulla just ventral to the emergent spinal accessory rootlet at the exact cross-sectional level of the obex; the current was passed for one minute with the point 5 mm. deep. Analgesia was then present on the opposite side, only from the costal margin down; so the electrode was inserted to a depth of 6 mm. As the last millimeter of the electrode was entering, the patient complained of pain in the contralateral side of the neck, but passage of current for 3 minutes caused no sensation (total passage, 6.5 minutes, at 3 ma.). However, the patient then had analgesia up to the lower border of the ramus of the mandible. This level had receded to the fourth cervical segment 10 months later, leaving severe hypalgesia over the second and third cervical segments.

In patient L. F. the electrode at the same site in the bulb was used first to carry the 30-per-second, 1-msec., square-wave signal from a Grass stimulator to see whether we could utilize this method of checking the electrode position. At the threshold of 2 volts a diffuse sensation over the whole body, "like a little electric shock," was produced; this was not more sharply localized at 5 volts, so that no precise information as to the site of the electrode placement was derived. At the same spot (5 mm. deep) application of the lesion-making current for 2.5 minutes produced analgesia on the other side over the body from the fifth cervical segment down. After another two minutes at 6 mm. depth the analgesia rose only one more segment. Application for another minute at 6 mm. depth did not change the level of analgesia (total, 5.5 minutes, at 3 ma.). During the second period of application of current the patient complained rather halfheartedly of a shock-like sensation felt diffusely throughout much of his body. During the first and third periods there was no subjective sensation. The pulse rate and blood pressure dropped during each of the three periods of application of current but rose nearly to the previous levels each time before or just after the end of this period (Fig. 1). During the two months which this man survived he was free of his pain, which had been in the shoulder and upper limb, and maintained analgesia into the fifth cervical segment. Necropsy revealed a well-placed lesion 4 mm. in diameter, with its inner border almost reaching the medical lemniscus (Fig. 2).

The next two experiences were discouraging. In Patient S. S., a woman of unusual cooperation on the operating table, the point of the electrode was inserted at the same spot as in the two previous patients. At a depth of 5.5 mm., passage

of current for three minutes produced no demonstrable hypalgesia, and at a depth of 6.5 mm. for another three minutes it still yielded no loss to pinprick stimulation. During the making of the second lesion, the blood pressure rose gradually from 150/70 to 200/80 over five readings in the three minutes, but there were no subjective sensations. The electrode was withdrawn until its point was at a depth of

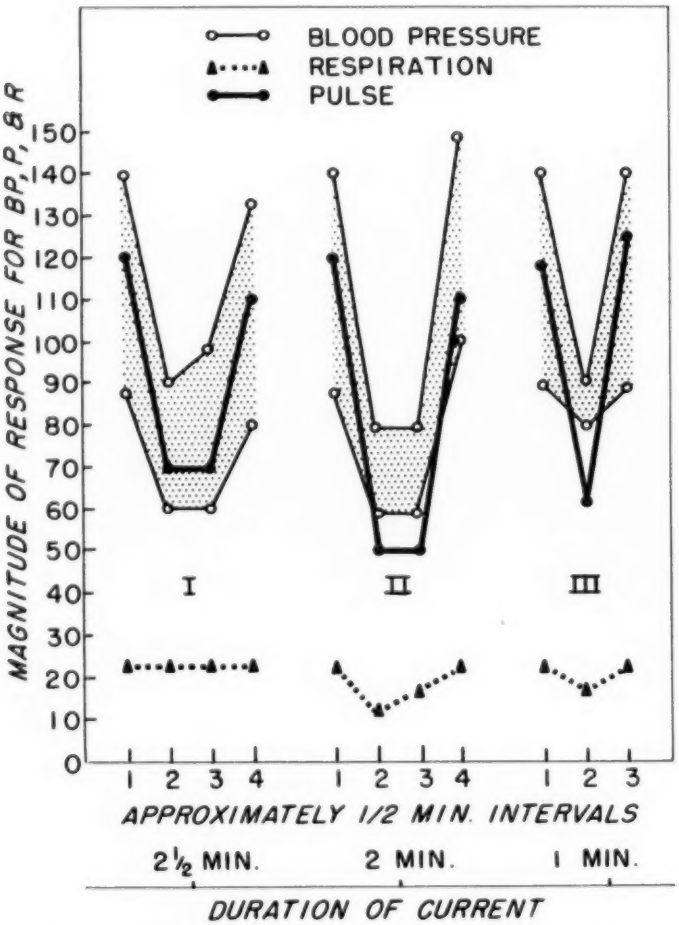

Fig. 1. (Patient L. F.).—Effects on pulse rate, respiration rate, and blood pressure of an electrode inserted 6 mm. into the bulb at the level of the obex, passing 3 ma. of current. Note the return of pulse rate and blood pressure toward normal levels before the cessation of current flow.

only 3.5 mm and after another passage of current of 3 ma. for three minutes there was profound hypalgesia, confined to the contralateral arm. With the point of the electrode 2.5 mm. deep, a final 3-minutes[1] stimulation yielded analgesia of the lower limb (total, 12 minutes, at 3 ma). About 90 minutes was devoted to this

lesion-making and testing phase of the operation, and we are confident of the reliability of the responses. Testing on the first to the sixth postoperative days showed much more extensive analgesia, from just above the clavicle over all lower segments contralateral to the lesion, and complete relief of pain until death, on the seventh postoperative day. Necropsy showed an essentially nonhemorrhagic lesion, larger than necessary, involving the upper half of the inferior olivary nucleus, as well as the appropriate region of the reticular formation just dorsal to this; it was 6 mm. wide by 5 mm. high in the cross section in which it was maximal (Fig. 3). It is likely that the additional destruction of the bulbar tissue contributed to the

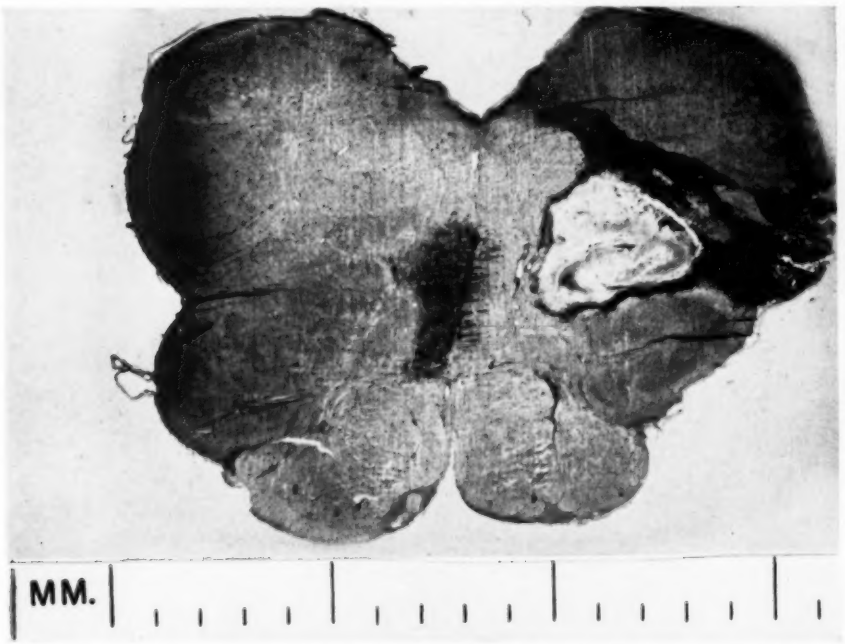

Fig. 2.—Cross-sectional extent of the lesion in Patient L. F. after 2½ minutes of electrocoagulation with a current of 3 ma. at a depth of 4 to 5 mm. The patient was free from pain and succumbed to his original disease two months after operation. The lesion is confined to the right half of the bulb. The area of total destruction is nearly clear and is about 3 cm. in diameter. Dark-staining areas to the left of the midline represent artifacts of the Marchi method.

patient's death, from extensive carcinoma. A striking feature in this case was the long delay in development of analgesia following the passage of the current.

Patient A. S. was unable to tell us where he felt pain when stimulated with an electrode tip 6 mm. deep in the bulb at the cross-sectional level of the obex. When we changed to the lesion-making current, bringing it up rapidly to 3 ma., as we had done in each previous case, the patient abruptly extended all four limbs. They relaxed when the current was promptly shut off. The electrode position seemed to be correct; so the current was raised to 3 ma. gradually over 20 seconds and held there for 110 seconds. The patient made no special movements; however, he

was much less responsive to testing thereafter. Two more lesions were made for two minutes each at depths of 4 and 2 mm., respectively (total, six minutes, at 3 ma.). During each of the three periods there was a rise in blood pressure of 15 to 25 mm. Hg systolic and 6 to 14 mm. Hg diastolic. Prior to the flow of current the blood pressure ranged from 174 to 190 systolic and 90 to 94 diastolic. Changes in pulse and respiration rates were less striking, but there was a slight rise in each of the three periods. After these lesions were made, the patient remained stuporous

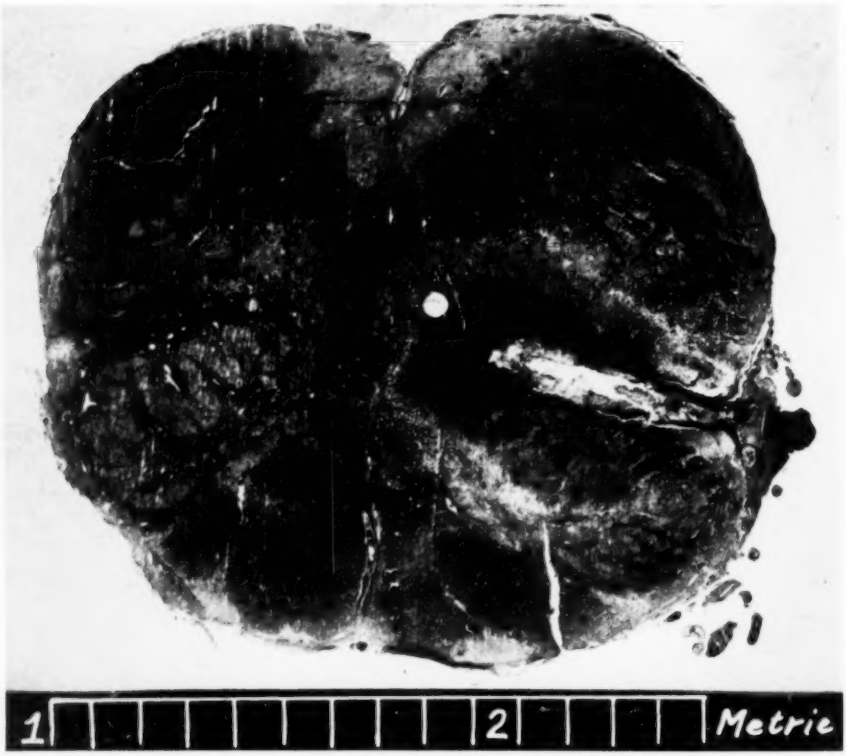

Fig. 3.—Cross-sectional extent of the lesion after 12 minutes of electrocoagulation at a current of 3 ma., at depths of 2, 3, 4, and 5 mm., for 3 min. each. Analgesia was produced to the clavicle, or the third and fourth cervical segments. The patient (S. S.) succumbed on the seventh postoperative day, partly because of the large brain-stem lesions.

and died a few days later. Autopsy disclosed a massive, deeply hemorrhagic spherical lesion, 9.5 mm. in diameter, occupying the inferior three-fifths of one side of the medulla (Fig. 4). The center of the lesion was at the cross-sectional level of the obex, about 5 mm. deep. The surface of the medulla looked normal, so bleeding must have started deep at the electrode site. There was no inkling of this bleeding at the time the electrode was withdrawn at operation.

Prior to this operation we used our electrode on Patient J. S. for a mesencephalic tractotomy, inserting it 4 mm. deep, 1 mm. dorsal to the lateral mesen-

cephalic sulcus. Interrupted square-wave electrical stimuli at this site, up to 10 volts, at a rate 30 per second, and 1 msec. in duration, caused no pain anywhere. The direct current was then applied for two minutes at 3 ma. The electrode was next shifted to two other positions (one 1 mm. ventral to, and the other 1 mm. deeper than, the original point), where a similar current was again applied for two minutes. She then showed hypalgesia of her contralateral forearm. The electrode was inserted 2 mm. dorsally to a depth of 4 mm., and it passed so readily ventrally to join the previously formed tract that no current was applied (total, six minutes, at 3 ma.). Later that day she showed analgesia from the top of the

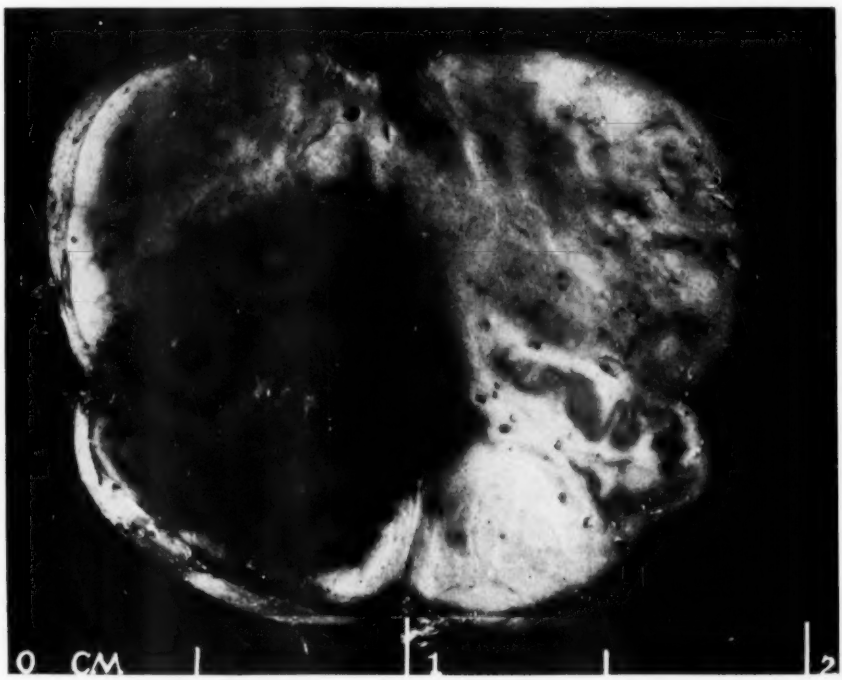

Fig. 4.—Massive medullary lesion produced in Patient A. S., who died several days after the operation, at which a current of 3 ma. was passed for two minutes at depths of 2, 4, and 6 mm., at the level of the obex.

head to the costal margin; two weeks later there were some hypalgesic areas in this zone, but she remained almost free from her original pain in the head, neck, and shoulder until death, five months after the operation.

II. *Animal Experiments.*—The initial animal experiments were begun on dogs and cats. The site of the first lesions was the medullary bulb, and factors of current were manipulated so as to approximate the operative conditions in man. Many of the early experiments, however, did not contribute useful information. The lesions varied unpredictably in size and shape, and some lesions were not found after careful search with use of the ordinary staining techniques.

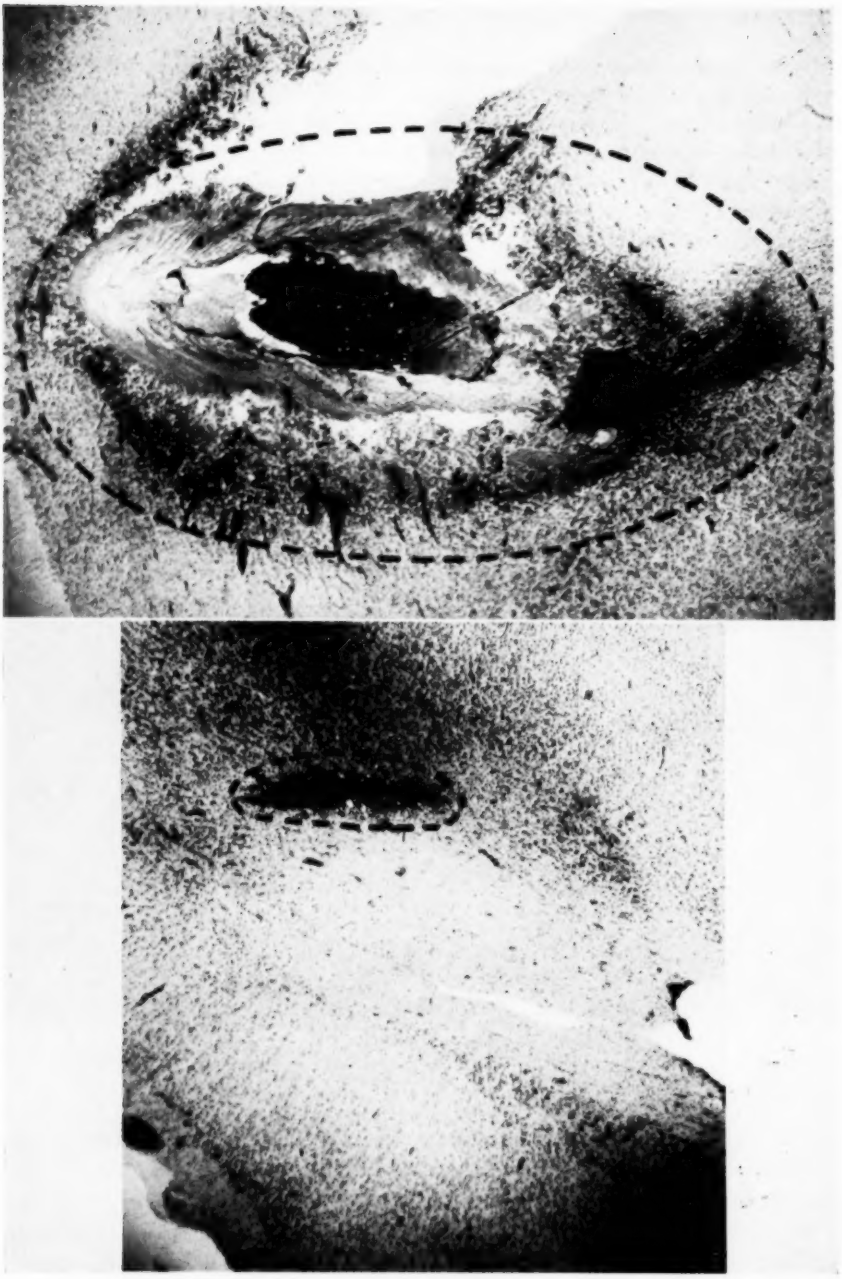

Fig. 5.—Maximal cross-sectional area of two lesions in the cerebral white matter of cats, at the same magnification. Both lesions were made by a current of 5 ma. passed for 10 seconds. As seen with stains for iron, the deposit of iron is usually central, in a well-circumscribed lesion, surrounded by gliosis and inflammatory reaction, and sometimes hemorrhage.

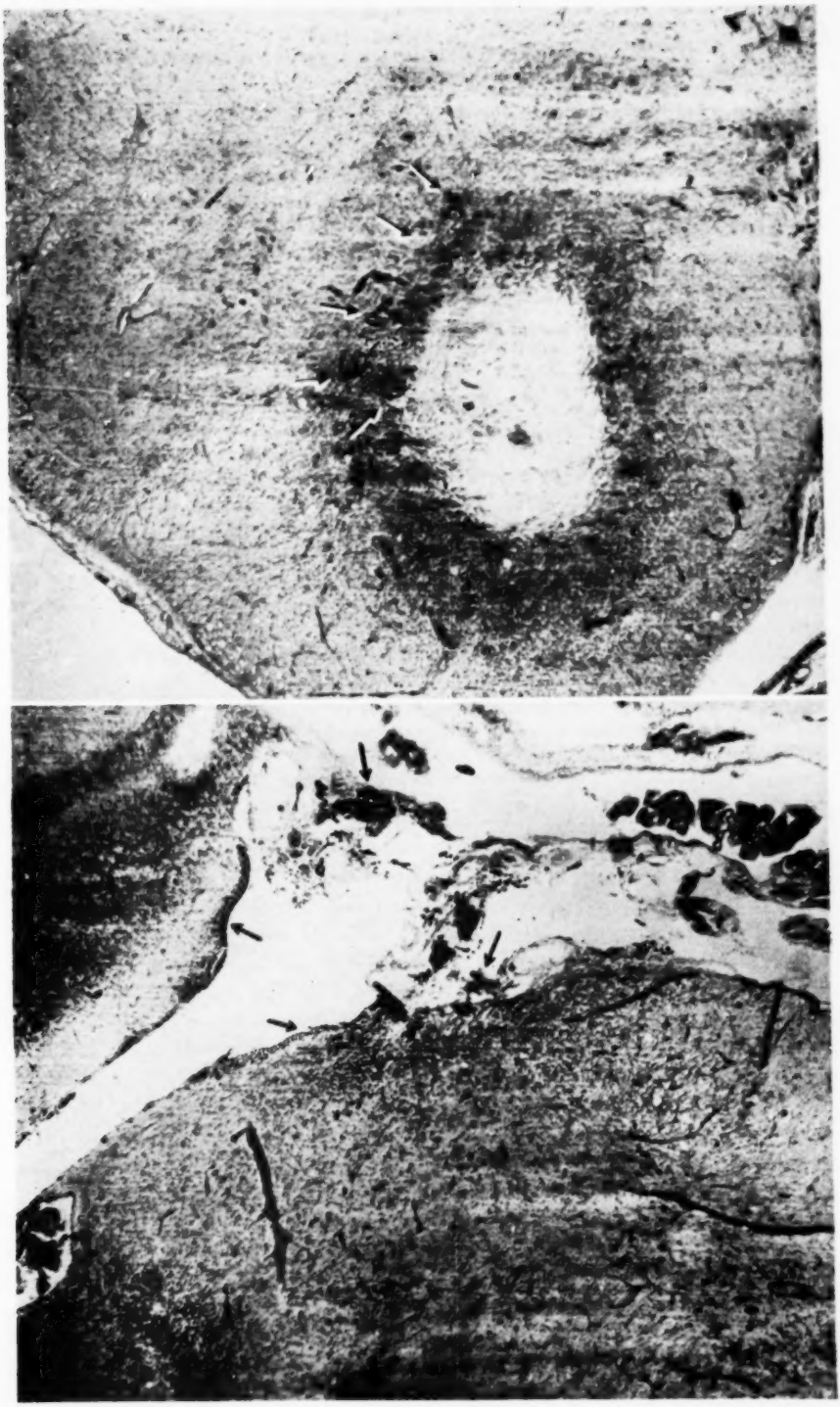

Fig. 6.—Exact position of blue-staining iron pigment described, with India ink, from colored transparencies of the two sections. The upper section is that of a well-circumscribed lesion within the brain stem made by passage of current at 3 ma. for 30 seconds. The lower section, at the same magnification, shows the results of application of 3 ma. of current for 60 seconds from an electrode whose tip was near the floor of the fourth ventricle. Iron pigment has spread widely, subpially and into arachnoidal granulations, without making a well-circumscribed lesion.

It was decided to vary the staining technique, site of lesion, and kind of electrode used. Various metals were substituted for the Magoun nichrome electrodes, including platinum, without much success. Stainless steel electrodes were finally chosen because they deposited iron, which was easily detectable with specific stains, and they possessed tips which were readily ground to suitable smoothness. The cerebral white matter was chosen as the site of the lesions because it offered sufficient room for several adequately separated lesions, and thus more data could be garnered from one experiment. An additional Berlin blue method for staining iron was used to detect not only the site of the lesion but also the major channels of current flow, as seen by characteristic deposits.

The stainless steel electrode (guage No. 20) was insulated with lacquer to within 1 mm. of the tip and checked with a voltmeter and in electrolytic solution to be sure that only the tip remained uninsulated. The ammeter on the Goodwin-Stein D.C. lesion maker was calibrated on several occasions to insure a constant accurate output of current.

The lesion-making current was attained at the maximum speed which would not induce a "make-shock" and maintained without variation during the time of destruction. Occasionally at 5 ma. destroyed tissue would collect on the uninsulated tip and increase the local resistance around the electrode, thus increasing the voltage necessary to maintain the desired current. (This datum was apparent from the voltmeter on the lesion maker.) Scraping the uninsulated portions of the electrode free of debris between lesions circumvented this difficulty.

The lesions were made at sterile operations, and the animals were killed from 2 to 18 days thereafter. Sample and serial histological sections were then made, using both routine and iron stains.

Seventy-two lesions were made in the cerebral hemispheres of 10 cats and 3 dogs. A 1 to 5 ma. current was used at times ranging from 10 seconds to 4 minutes. The results of these experiments and of two others on the brain stem are listed in the accompanying Table. The size of the lesions, indicated in millimeters, represents the maximum perpendicular diameter of the lesion. When the longitudinal diameter exceeded the other diameters, it was listed preceding the other two. If it was smaller than the others, it was not tabulated.

As can be seen from the Table, the variability in the size of these lesions was even greater than that seen in our human material,[5] and constancy was not achieved, even with short durations of current. For example, at 5 ma. and 10 seconds, one lesion was 4 by 7.2 mm. in maximal cross-sectional area, whereas another lesion at these same parameters measured 1.4 by 1.5 mm. At longer durations the lesions varied even more. At 3 ma. and 2 minutes the largest lesion in one experiment measured 30 by 6.4 by 12 mm., and the smallest, 7 by 4 by 3.2 mm. The presence of tiny blood vessels in some lesions tended to result in their taking erratic forms. Current flow, as ascertained by the deposit of iron pigment, would often surround neighboring vessels, resulting in thrombosis and extensive disruption of brain tissue about them. Even those lesions, however, confined to avascular portions of white matter showed a variability of several hundred per cent in area (Fig. 5). It is apparent that factors in addition to the obvious variations in the substrate of the lesion are important in producing the wide variations in the size of the lesions. It is interesting to note, moreover, that the quantitative deposition of iron pigment, as visualized with the aid of iron stains, is not always correlated with the size of the area destroyed. Current reaching the subarachnoid space, for example, tends to deposit iron widely without severely disrupting cerebral tissue (Fig. 6).

5. Sweet, W. H.; Nilges, R., and Mark, V. H.: Results of Electrosurgical Performance of Bulbar and Mesencephalic Tractotomies, read before the Harvey Cushing Society, April 27, 1951.

Summary of Experimental Lesions Made in Cats and Dogs*

Animal Designation	Time of Killing, Days	Current; Ma.	Time, Passage	Size of Lesion, Mm.	Site of Lesion
M- 7 (cat)	11	1	60 sec.	1.57 by 2.37	Cerebral white matter
M- 5 (cat)	18	3	30 sec.	2.39 by 2.53	Brain stem at the region of vestibular nucleus
M- 6 (cat)	4	3	30 sec.	Tissue disruption but no Fe pigment	Superior cervical cord
M- 7 (cat)	11	3	30 sec.	1.19 by 4.35	Cerebral white matter
M-28 (cat)	11	3	30 sec.	7.2 by 1.6	Cerebral white matter
		3	30 sec.	.....	Cerebral white matter
		3	30 sec.	4 by 5.6	Cerebral white matter
		3	30 sec.	2.4 by 3.4	Cerebral white matter
		3	30 sec.	1.2 by 1.6	Cerebral white matter
		3	30 sec.	2.8 by 1.3	Cerebral white matter
		3	30 sec.	3.8 by 1.28	Cerebral white matter
		3	30 sec.	9.6 by 1.2	Cerebral white matter
		3	30 sec.	0.8 by 0.6	Cerebral white matter
M-31 (cat)	10	3	30 sec.	14 by 4.4	Cerebral white matter
		3	30 sec.	5.2 by 2.9	Cerebral white matter
		3	30 sec.	2.9 by 3.2	Cerebral white matter
		3	30 sec.	1.2 by 6.4	Cerebral white matter
		3	30 sec.	5.6 by 1.6	Cerebral white matter
		3	30 sec.	1.7 by 4.3	Cerebral white matter
		3	30 sec.	1.6 by 4.8	Cerebral white matter
		3	30 sec.	1.6 by 3.2	Cerebral white matter
M- 5 (cat)	18	3	60 sec.	2.7 by 1.18	Brain stem at region of vestibular nucleus
M- 7 (cat)	11	3	60 sec.	2.37 by 2.37	Cerebral white matter
M-14 (dog)	2	3	2 min.	3.2 by 4.8	Hypothalamus
		3	2 min.	4.8 by 5.6	Hypothalamus
M-15 (dog)	2	3	2 min.	2.6 by 3.2	Hypothalamus
		3	2 min.	Small spot Fe around thrombosed vessel	Hippocampus
M-17 (cat)	11	3	2 min.	5.2 by 4	Cerebral white matter
		3	2 min.	2.8 by 3.4	Cerebral white matter
		3	2 min.	3.6 by 4	Cerebral white matter
		3	2 min.	3.2 by 5.6	Cerebral white matter
M-25 (cat)	10	3	2 min.	14 by 7.2 by 6.4	Cerebral white matter
		3	2 min.	12 by 4 by 6.4	Cerebral white matter
		3	2 min.	7 by 4 by 3.2	Cerebral white matter
M-26 (cat)	10	3	2 min.	33 by 6.4 by 12	Cerebral white matter
		3	2 min.	0.6 by 0.8	Cerebral white matter
M-27 (cat)	10	3	2 min.	4.8 by 6.4	Cerebral white matter
		3	2 min.	4.8 by 2.4	Cerebral white matter
		3	2 min.	3.2 by 12 blood vessel coagulation (iron) + 4.8 by 4.8 tissue disruption near area of iron deposit	Cerebral white matter
		3	2 min.	20 by 6.4 by 5.6	Cerebral white matter
		3	2 min.	10 by 4.8 by 6.4	Cerebral white matter
M-13 (dog)	2	3	4 min.	Blue pigment, 5.2 by 4, 2.0 by 3.2 and 4.8 by 6.4	Hypothalamus
M- 7 (cat)	11	5	5 sec.	4.75 by 2.9 in blood vessel with consolidated hemorrhages	Cerebral white matter
M-29 (cat)	11	5	10 sec.	3.2 by 5.1	Cerebral white matter
		5	10 sec.	2.2 by 5.6	Cerebral white matter
		5	10 sec.	8 by 2.4	Cerebral white matter
		5	10 sec.	4.8 by 1.6	Cerebral white matter
		5	10 sec.	2 by 3.2	Cerebral white matter
		5	10 sec.	1.4 by 1.5	Cerebral white matter
		5	10 sec.	5.6 by 1.6	Cerebral white matter
M-30 (cat)	10	5	10 sec.	4 by 7.2	Cerebral white matter
		5	10 sec.	3.3 by 1.4	Cerebral white matter
		5	10 sec.	1.6 by 3.6	Cerebral white matter
		5	10 sec.	5.2 by 3.7	Cerebral white matter
		5	10 sec.	4.5 by 2.8	Cerebral white matter
		5	10 sec.	4.6 by 2.8	Cerebral white matter
		5	10 sec.	4.8 by 2.8 ⎫ side by	Cerebral white matter
		5	10 sec.	3.6 by 4 ⎭ side	
		5	10 sec.	4.4 by 8	Cerebral white matter
M-22 (cat)	3	5	2 min.	8 by 3.2 by 8	Cerebral white matter
		5	2 min.	Starts in blood vessel in sulcus, 11 by 1.6 by 8	Cerebral white matter
		5	2 min.	30 by 6.4 by 6.4	Cerebral white matter
M-25 (cat)	10	5	2 min.	20 by 4.8 by 4	Cerebral white matter
		5	2 min.	2.4 by 4.15	Cerebral white matter
		5	2 min.	Irregular specks of Fe	Cerebral white matter
M-26 (cat)	10	5	2 min.	12 by 1.2 into sulcus	Cerebral white matter
		5	2 min.	18 by 4.5 by 4.8	Cerebral white matter

* The size of the lesion, as tabulated in millimeters, represents the maximal cross-sectional dimension of the lesion. When the longitudinal dimension was larger than either dimension in cross section, it was included as the first figure in the tabulation; if it was smaller than the other two, it was left out.

COMMENT

Prior to our work, Glees and Wall [6] (1946) demonstrated disturbing variations in size of lesions produced electrolytically. Whittier and Mettler [7] (1949) performed 120 stereotaxic operations upon 80 rhesus monkeys and found fulgurative lesions "varied unpredictably in size and shape, being determined by uncontrolled variables of electrolysis (gas volumes, polarization) and anatomy (tissue planes, vascular interruption)."

In their recently prepared manuscript, which we had the privilege of studying, Carpenter and Whittier [8] give data not only on methods using direct current at anodal electrodes, but on chemical, mechanical, and high frequency electrical methods as well. They concluded that anodal unipolar lesions produced by direct current give the most profitable fulgurative lesions, and that if electrode tips are smoothly and evenly ground and a current of 5 ma. or less is employed for less than 30 seconds the size of the lesion will vary from 0.8 to 3.2 units on their lesion index. Our results make us less optimistic about this method, even with these precautions, and this paper is presented to serve as a warning to other workers in the field.

We have begun to experiment with two other methods of making small, discrete lesions in the central nervous system. The first involves the use of unipolar or bipolar, nonelectrolytic, radiofrequency current, and the second employs beta emitters of a short half-life, such as radioactive gold. Neither method has been used enough to bear comment at the present time.

CONCLUSION

Unipolar anodal electrolytic lesions are too variable for use in the brain stem or the diencephalon of man, and an essential corollary to the use of the stereotaxic method in man will be the development of a technique for making a reliable small lesion at the elected point.

Miss Janette Robinson assisted in making our histological preparations.

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MOBILIZATION OF GLUCOSE BY PHLORHIZIN IN PATIENTS WITH MENTAL DISORDERS

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AVAILABLE evidence indicates that utilization of carbohydrate may be impaired in patients with manic-depressive, involutional, and schizophrenic psychoses.[1] Information on the mobilization of glucose in such patients is incomplete. The rise in blood sugar following intramuscular injection of epinephrine is usually normal, or greater than normal, even in malnourished patients with severe neuroses or with manic-depressive or schizophrenic psychoses.[2] However, this observation elucidates only a portion of the entire process of glucose mobilization. The studies of Mirsky and associates[3] on changes in glucose in the blood and urine after injection of phlorhizin in man suggested that the use of that substance in patients with mental disease might afford information useful in the interpretation of the metabolic disorder commonly encountered in certain psychoses.

MATERIAL AND METHODS

Twelve patients, of ages ranging from 19 to 64, were studied; 8 were women. The diagnoses varied (Table); one patient (Gr) had diabetes in addition to a manic psychosis. Five patients were given electric shock therapy; four of these were studied again several days after the end of the course of treatment, while one (Gr) was studied in the midst of it. Seven patients were given insulin treatments and were studied again several days after the last treatment.

Observations were made on all patients before treatment; studies were made with phlorhizin two to five days after an epinephrine test for estimation of hepatic glycogen, as described elsewhere,[2] was carried out. The method of Folin and Wu[4] was used for estimation of blood sugar and that of Benedict[5] for determination of urinary sugar. Blood eosinophiles were counted,

From the Laboratory of Clinical Physiology, McLean Hospital, Waverley, Mass., and the Department of Medicine, Harvard Medical School.

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2. Altschule, M. D.; Siegel, E., and Mora-Castaneda, F.: Significance of Rise in Blood Sugar Level After Injection of Epinephrine in Mental Disease, A. M. A. Arch. Neurol. & Psychiat. **65**:589, 1951.

3. Mirsky, I. A.; Korenberg, M.; Nelson, N., and Nelson, W. E.: The Hepatic Glycogen Reserves in Diabetes Mellitus, Endocrinology **28**:358, 1941.

4. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. 2: Methods, Baltimore, Williams & Wilkins Company, 1932, p. 456.

5. Benedict, S. R.: The Detection and Estimation of Glucose in Urine, J. A. M. A. **57**:1193, 1911.

as described previously,[6] before and at intervals after the injection of phlorhizin, and estimations of the blood glutathione level were made at the same time, as described elsewhere.[7]

After it was discovered that the method of giving phlorhizin recommended by Mirsky and associates,[3] that is, intravenous injection of the drug dissolved in hot strong alkali, was not

Data on Mobilization of Glucose in Patients with Mental Disease After Injection of Phlorhizin

Patient	Sugar Excreted, Gm./Kg.	Blood Sugar, Mg./100 Ml.			Maximal Rise After Epinephrine	Blood Eosinophiles, % Fall	Comments
		Initial	Average During	Maximal Fall			
Li	0.23	82	76	24 (4)	48	80	Schizophrenia
	0.14	94	92	6 (3, 4)	43	76	6 wk. later: improvement after insulin therapy
In	0.31	84	84	6 (3, 4)	36	8	Schizophrenia
	0.30	95	87	15 (4)	51	18	7 wk. later: improvement after insulin therapy
Mc	0.23	101	90	19 (5)	68	71	Schizophrenia
	0.28	108	104	12 (4)	65	74	9 wk. later: beginning relapse after insulin therapy
Ra	0.29	81	87	0	86	39	Schizophrenia
	0.28	102	90	24 (4)	48	34	10 wk. later: improvement after insulin therapy
Go	0.30	98	95	6 (3, 4, 5)	30	46	Schizophrenia
	0.40	142	113	42 (2)	63	76	4 wk. later: improvement after insulin therapy
Me	0.33	92	91	4 (2)	108	71	Neurosis
	0.25	84	80	8 (2, 4)	50	52	7 wk. later: improvement after insulin therapy
Bo	0.38	86	86	2 (3, 4)	27	77	Manic-depressive, manic, psychosis
	0.38	98	95	14 (4)	49	30	6 wk. later: improvement after insulin therapy
Bu	0.25	74	66	22 (5)	6	52	Schizophrenia
	0.25	84	82	10 (5)	32	44	5 wk. later: improvement after electroshock therapy
We	0.34	113	86	13 (2, 4)	9	30	Paranoid condition
	0.38	98	81	34 (5)	34	54	6 wk. later worse
	0.24	92	93	10 (2)	31	36	3 wk. later: improvement after electroshock therapy
Ba	0.21	90	88	18 (5)	..	53	Manic-depressive psychosis, depressed type
	0.14	92	87	12 (3)	..	68	3 wk. later: improvement after electroshock therapy
	0.22	113	110	5 (2)	..	58	11 wk. later: relapse
	0.23	98	97	14 (2)	..	79	4 wk. later: improvement after electroshock therapy
Fa	0.14	94	91	8 (2)	..	83	Involutional psychosis
	0.16	94	86	14 (2)	..	67	5 wk. later: improvement after electroshock therapy
Gr	0.90	336	277	124 (5)	..	..	Manic-depressive psychosis, manic type; diabetes mellitus
	1.42	316	286	53 (2)	..	..	2 wk. later: during electroshock therapy
Pe	0.27	90	86	10 (4)	90	33	Neurosis

satisfactory, it was decided to give the phlorhizin intramuscularly dissolved in propylene glycol. Accordingly, 1 gm. of the drug in 5 ml. of solvent was given at the start of the experiment, and 1 gm. an hour later. Samples of urine were collected 90 minutes before, a minute before, and

6. Altschule, M. D.; Siegel, E. P.; Restaino, R. M., and Parkhurst, B. H.: Blood Eosinophilic Leucocytes in Mental Disease, A. M. A. Arch. Neurol. & Psychiat. **67**:228, 1952.

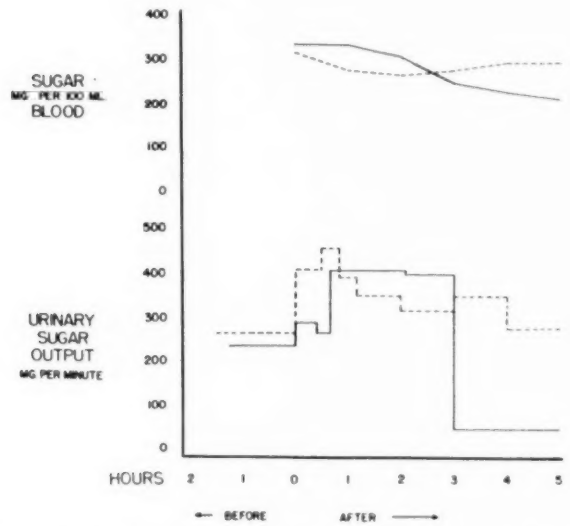
7. Henneman, D. H., and Altschule, M. D.: Immediate Effects of Shock Therapies, Epinephrine and ACTH on Blood Glutathione Level of Psychotic Patients, J. Appl. Physiol. **3**:411, 1951.

hourly up to five hours after the first injection; the patients were not permitted food all morning but were encouraged to drink water freely. Samples of venous blood were taken before and hourly up to five hours after the first injection of phlorhizin.

OBSERVATIONS

Urinary Sugar.—The urinary output of sugar in the five hours of the test period was between 0.14 and 0.38 mg. per kilogram of body weight for the untreated non-diabetic patients; one untreated patient studied on two occasions, six weeks apart, gave values of 0.34 and 0.38 gm. during these two tests. Another patient studied before treatment and again in relapse, three months later, excreted, respectively, 0.21 and 0.22 mg. of glucose per kilogram of body weight.

The rate of excretion of sugar during the five-hour period showed small fluctuations, except in the diabetic patient, for whom the rate of excretion fell sharply toward the end of the test (Chart). The second test made on the diabetic patient,



Changes in blood sugar and in urinary output of sugar in a psychotic patient with diabetes after injection of 2.0 gm. of phlorhizin. The solid lines indicate observations made before treatment, and the broken lines, those made after the third of a series of 11 electric shock treatments.

five days after the third of a course of 11 electric shock treatments, resulted in an excretion of 1.42 gm. per kilogram in five hours, the curve remaining relatively flat (Chart).

After a course of electric shock treatments, repetition of the tests yielded values for excreted glucose ranging from 0.14 to 0.23 gm. per kilogram of body weight, as compared with the pretreatment values of 0.16 to 0.38 gm. per kilogram of body weight: No significant changes occurred in four of five patients. One patient (Ba), studied during two psychotic episodes, showed a decrease of 0.7 gm. per kilogram after the first course of electric shock therapy and no change after the second course.

After a course of insulin treatments (patients ambulatory) the excretion of glucose following injections of phlorhizin was between 0.14 and 0.40 gm. per

kilogram in five hours. Three patients showed no significant difference between the results obtained after and those obtained before treatment; two showed small increases, and the other two small decreases, after treatment.

Blood Sugar.—In the untreated nondiabetic patients the maximal fall in blood sugar after injection of phlorhizin was between 0 and 34 mg. per 100 ml. of blood; after treatment it was between 5 and 42 mg. per 100 ml. of blood. The maximal fall was more than 10 mg. per 100 ml. in 5 of 13 instances before treatment and in 9 of 12 after treatment. The greatest fall occurred at different times in different patients, and in several instances the lowest level of blood sugar occurred several times as the levels fluctuated. In the diabetic patient the maximal falls in blood sugar were far greater than those in the nondiabetic subjects.

Blood Glutathione.—No significant change in the glutathione level was noted during any experiment.

Blood Eosinophiles.—Decreases in blood eosinophile counts four hours after the first injection of phlorhizin were between 8 and 83%; in 16 of 26 experiments the decreases were greater than 50% of the control values.

Rise in Blood Sugar After Epinephrine.—In 17 of 19 experiments the rise in blood sugar after epinephrine was normal, while in 2 (Patients Bu and We) low values were obtained. There was no correlation between the glycemic reaction to epinephrine and the changes in carbohydrate metabolism observed in the same patient after the injection of phlorhizin.

COMMENT

Rapid loss of glucose from the body after the injection of phlorhizin stimulates glycogenolysis and gluconeogenesis. The latter is influenced by adrenocortical activity, and it is therefore interesting that eosinopenia occurred in a majority of the experiments described here.

The effect of phlorhizin is to make glucose a nonreabsorbable substance. However, the amount of glucose excreted in the urine during the test period affords little information concerning mobilizable carbohydrate in the body, since the urinary glucose output is proportional to the blood glucose level; this is shown by statistical analysis of the data of Mirsky and associates[3] and by the findings for two patients in the present study (Gr and Go, Table). In addition, the fall in blood sugar at any given rate of glucose mobilization must be proportional to the initial concentration of sugar in the blood. These considerations render both the fall in the blood sugar level and the amount excreted in the urine useless for interpretations concerning rates of mobilization of body carbohydrate except within narrow levels of blood sugar.

It is evident from this discussion that the changes after injection of phlorhizin cannot be used for comparison of available carbohydrate stores in normal subjects and those of diabetic patients with high blood sugar levels. However, the use of the test in the present study is valid, since almost all the subjects had normal initial blood sugar levels. The amounts of glucose excreted by the nondiabetic patients before and after treatment were in the range observed in normal subjects.[3] In the latter, mobilization of glucose keeps pace with this increased excretion; blood sugar levels show negligible changes.[3] On the other hand, in patients with mental disease in this study abnormal decreases in blood sugar were common in spite of normal

control levels; i. e., mobilization lagged behind excretion of glucose. This phenomenon was not due to malnutrition, since it was even commoner after treatment, when the state of nutrition in all the patients was much improved. The influence of malnutrition was observed only in the diabetic patient (Gr), in whom a fall in blood sugar level of 124 mg. per 100 ml. was found before treatment, as compared with a much smaller, but still abnormal, fall of 53 mg. per 100 ml. during treatment; the slighter fall in blood sugar level occurred in spite of a much greater excretion of sugar, showing that some improvement in nutrition had occurred (Chart).

The data of the present study suggest that mobilization of glucose for maintenance of a normal blood sugar level may be abnormal in patients with mental diseases. The nature of this defect is not evident; however, in 10 of 14 instances in which abnormal decreases in blood sugar occurred, the excessive fall occurred early in the period of the test and was partly or completely abolished by the end of the experiment. This finding suggests that the abnormality in mobilization is merely temporal. Epinephrine tests, made on 10 of the patients showing sluggish mobilization of glucose after phlorhizin, showed that hepatic glycogenolysis was normal or increased in 8 of them. It is probable, therefore, that the retardation of glucose mobilization observed in some patients with mental disease is not in epinephrine-induced hepatic glycogenolysis, but involves other glycogenolytic processes or gluconeogenesis or both.

SUMMARY AND CONCLUSIONS

Changes in carbohydrate metabolism after injection of phlorhizin were studied in patients with mental disease before and after treatment. The amount of glucose excreted was in the normal range. However, changes in blood sugar level during the test indicate that mobilization of carbohydrate is sluggish in some patients; this abnormality apparently involves processes other than epinephrine-induced hepatic glycogenolysis.

MORPHOLOGY OF THE TESTES IN SCHIZOPHRENIA

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TESTES FUNCTION IN SCHIZOPHRENIA: REVIEW OF LITERATURE

SINCE the early conceptualizations of dementia praecox, or, as it is now more commonly designated, schizophrenia, by Kraepelin [1] and Bleuler,[2] attention has been directed toward the possible occurrence of endocrine abnormalities during the course of the illness. Leading to this interest were the early observations of striking abnormalities in the psychosexual field manifest prior to and during the course of the illness. Heterosexual object relations are inadequate; marriage occurs infrequently, and homosexuality is common, both in latent and in overt forms.[3]

These clinical abnormalities involving psychosexuality led to postulations and investigations of possible alterations in gonadal function and structure in schizophrenia. Kraepelin [1] originally considered that dementia praecox was attributable to an autointoxication arising in the gonads, and, although he later relinquished this idea, he continued to believe that a metabolic intoxication caused the illness.

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Dr. R. H. Flocks, of the Department of Urology of the State University of Iowa School of Medicine, obtained the biopsy specimens.

Dr. Max E. White, Superintendent, Independence Mental Health Institute, Independence, Iowa, made available the institutionalized patients used in this study.

These data are taken in part from a thesis submitted in partial fulfilment of the requirements for the degree of Master of Science, in the Department of Psychiatry and the Graduate College (Dr. Tourney).

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2. Bleuler, E.: Dementia Praecox or the Group of Schizophrenias, translated by J. Zinkin, New York, International Universities Press, Inc., 1950.

3. Gibbs, C. E.: Sex Development and Behavior in Male Patients with Dementia Praecox, Arch. Neurol. & Psychiat. **9**:73, 1923. Lewis, N. D. C., and Blanchard, R.: Clinical Findings in "Recovered" Cases of Schizophrenia, Am. J. Psychiat. **11**:481, 1931. Rennie, T. A. C.: Analysis of 100 Cases of Schizophrenia with Recovery, Arch. Neurol. & Psychiat. **46**:197, 1941. Hoskins, R. G.: Psychosexuality in Schizophrenia: Some Endocrine Considerations, Psychosom. Med. **5**:3, 1943.

Mott and co-workers [4] made the first important contributions to the histopathology of the testes in schizophrenia during the years from 1919 to 1923. Using autopsy material from 27 schizophrenic patients and comparing this with similar material from men with other mental illnesses, they defined three stages of regressive atrophy of the testes as characteristic of schizophrenia. They described the first stage as showing diminution in tubular size, with a reduction in the number of spermatocytes, spermatids, and spermatozoa; the Sertoli cells were empty of lipid and more distinct than normal, and the basement membranes showed early thickening. The second stage was characterized by the occurrence of atrophy in most tubules, marked thickening of the basement membranes, and little evidence of mitotic activity in the spermatogonia and spermatocytes. Fatty degeneration of the spermatozoa, pronounced changes in the Leydig cells, and an increase in the amount of interstitial material were described as other significant histological features. In the third stage, Mott stated, few germ cells were seen; the tubules were strikingly atrophic, and no normal Leydig cells were present. The severity of the testicular changes was reported to correlate with the clinical stage of the illness, the chronic forms demonstrating the severer atrophy. Mott postulated the existence of a primary defect of the gonads in schizophrenia, resulting in a disordered hormonal balance and, in turn, abnormal cerebral function.

In 1923 Lewis [5] described similar findings in autopsy material. Ten of 18 schizophrenic patients were said to exhibit complete absence of spermatozoa, while the others showed earlier stages of regressive atrophy of the testes. There was, however, no correlation of the severity of the atrophy and the duration of the illness, as Mott had reported.

The aforementioned studies have been criticized by Morse [6] and Lewin.[7] They indicated that Mott and Lewis did not take into account the important factors of age, nutrition, terminal illness, and probable variations in the normal histology of the testis. In the study of 12 patients with dementia praecox, Morse found little or no evidence of primary atrophy of the testes. Lewin, in analysis of the data on 65 patients with mental illness, 16 of whom were suffering from schizophrenia, concluded [7]:

> Our data have led us to believe that in the dementia praecox material the changes in the spermatozoa and the basement membrane do not differ in character from those observed in other psychotic groups of similar age, and they are dependent on adventitious circumstances.

He found active spermatogenesis in patients with schizophrenia of 23 to 35 years' duration, their ages ranging from 59 to 75.

4. Mott, F. W.: Normal and Morbid Conditions of the Testes from Birth to Old Age in 100 Asylum and Hospital Cases, Brit. M. J. **2**:655, 698, and 737, 1919. Matsumoto, T.: Study of the Relation Between the Reproductive Organs and Dementia Praecox, J. Ment. Sc. **66**:414, 1921. Mott, F. W., and Prados y Such, M.: Further Pathological Studies in Dementia Praecox, Especially in Relation to the Interstitial Cells of Leydig, Proc. Roy. Soc. Med. **15**:1, 1922. Prados y Such, M.: Morbid Histology and Testes in Dementia Praecox, ibid. **15**:14, 1922. Mott, F. W.: Conditions of Sex Organs in Dementia Praecox, Encéphale **18**:73, 1923.

5. Lewis, N. D. C.: The Constitutional Factors in Dementia Praecox, with Particular Attention to the Circulatory System and to Some of the Endocrine Glands, New York, Nervous and Mental Disease Monographs, 1923, pp. 111-115.

6. Morse, M. E.: Pathological Anatomy of the Ductless Glands in a Series of Dementia Praecox Cases, J. Neurol. & Psychopath. **4**:1, 1923.

7. Lewin, B. D.: A Study of the Endocrine Organs in Psychoses, Am. J. Psychiat. **7**:391, 1927.

Kirby and Gibbs,[8] Tiffany,[9] and McCartney [10] reported findings similar to those of Mott and Lewis, but their series, again, were not adequately controlled, since they failed to take into account the variables discussed by Morse and Lewin.

Recent interest in this problem has been aroused by the work of Hemphill, Reiss, and Taylor.[11] Using the biopsy method of procuring testicular tissue, they studied 90 patients with schizophrenia and 25 patients with other mental illnesses. Supposedly, none of the patients were malnourished or suffering from physical illness or had given a history of gross gonadal defects. Hemphill and associates believed they had confirmed the occurrence of testicular atrophy in schizophrenia but disagreed in the main with the interpretation provided by Mott and his contemporaries with regard to the characteristics of the histological structure and the causation and pathogenesis of the changes. They reported that in schizophrenia the testicular changes varied from a slight reduction in spermatogenesis to gross atrophy. In the more severely damaged testes, they reported as characteristic features changes in the basement membrane, hyaline degeneration and arrest of spermatogenesis, progressive degeneration of the epithelial elements and eventual destruction of the tubules, sclerosis of the smaller blood vessels, little interstitial fibrosis, and inconstancies in the number of Leydig cells. They observed in many specimens an extremely advanced degree of atrophy, with collapse and fusion of the tubules as a hyaline mass and no cellular activity.

Hemphill and his co-workers reported the existence of an association between deteriorating schizophrenia and severe testicular atrophy but found that severe atrophy may be present in the earliest stages of the illness. The severest atrophy was noted when the onset of the illness occurred before the age of 20. They also reported that atrophy is characteristic only of the nonparanoid types of schizophrenia and that testicular function appeared normal in the paranoid type. The secondary sexual characteristics had developed satisfactorily in all cases. They believed that the cause of atrophy may be an endocrine disorder, with inadequate gonadotropin control, and noted [11b]:

> The atrophy of the testis can be accepted as reflecting one physiological abnormality, probably mediated by the pituitary or hypothalamus, which is an essential feature in the pathogenesis of the disorder. This would imply that an endogenous factor is the primary agent in the production of schizophrenia, and this to a large extent is in keeping with our experience.

Subsequently, Hemphill and Reiss [12] administered gonadotropic hormone of pregnant mares' serum to schizophrenic patients with testicular atrophy and

8. Kirby, G. H., and Gibbs, C. E.: Reproductive Glands and Mental Disorder, with Special Reference to Dementia Praecox, State Hosp. Quart. **6**:147, 1921.

9. Tiffany, W. J.: Pathological Changes of Testes and Ovaries in Dementia Praecox, State Hosp. Quart. **6**:159, 1921.

10. McCartney, J. O.: Dementia Praecox as an Endocrinopathy with Clinical and Autopsy Reports, Endocrinology **13**:73, 1929.

11. (*a*) Hemphill, R. E.; Reiss, M., and Taylor, A. L.: A Study of the Histology of the Testis in Schizophrenia and Other Mental Disorders, J. Ment. Sc. **90**:681, 1944. (*b*) Hemphill, R. E.: The Significance of Atrophy of the Testis in Schizophrenia, ibid. **90**:696, 1944. (*c*) Hemphill, R. E., and Reiss, M.: Experimental Investigations in the Endocrinology of Schizophrenia, Proc. Roy. Soc. Med. **41**:533, 1948.

12. Hemphill, R. E., and Reiss, M.: Serum Gonadotrophin and Testis Biopsy in Treatment of Schizophrenia, J. Ment. Sc. **91**:1, 1945.

reported improvement in the structure of the testis, although normal spermatogenesis was not achieved. No significant clinical change in the psychosis was produced.

After the present study had been completed, Blair and co-workers[13] reported 17 cases of schizophrenia in which they were unable to confirm the findings of Hemphill, Reiss, and Taylor. Their observations indicated that the histological abnormalities in the testes of schizophrenic patients were no greater than would be expected in a similar group of entirely normal potent men.

The present study recognizes the need for clarification of the issues raised by Mott and, later, by Hemphill, Reiss, and Taylor, since their observations and interpretations, and those of other students of the problem, are conflicting and do not provide a clearly defined solution to the question of testicular morphology in schizophrenia. In the present investigation, the testicular histology of both noninstitutionalized patients with relatively acute schizophrenia and institutionalized patients with chronic schizophrenia has been studied by utilization of bilateral testicular biopsies.

MATERIAL AND METHODS

Twenty-three typical schizophrenic patients were the subjects of this study. Sixteen of these patients were designated as noninstitutionalized, since they were studied shortly (within two weeks) after their first hospitalization for schizophrenia and none had had treatment for their illness. The remaining seven patients were designated as institutionalized, since all had been hospitalized for a number of years. None of the latter patients had received insulin coma therapy, electric convulsion therapy, or lobotomy during their hospitalization.

The nutritional status of all the noninstitutionalized patients was good; and although 7 of these 16 patients had some loss of appetite during the course of the illness, this disturbance was usually transitory and had little or no effect on their over-all nutritional condition. The patients showed no evidence of organic disorder or of gross gonadal defects. The age range for these patients was 19 to 39, with a mean of 24.7 years. The date of onset of the illness was estimated by the first notable changes in the patient's usual personality structure, as observed by relatives and friends. The mean duration of illness for these patients prior to testicular biopsy was 17 months, but the illness of 10 patients was of less than 6 months' duration. On the whole, the noninstitutionalized patients presented little or no deterioration prior to the time of testicular biopsy. The clinical data on the noninstitutionalized patients are summarized in Table 1.

The seven institutionalized patients were in satisfactory nutritional status, although six had had an episode of capricious appetite at some time during the course of the illness, in whch they refused to eat, and several patients lost up to 20 lb. (9.1 kg.) in weight during such periods. These patients presented neither organic disorder nor gross gonadal defects. Deterioration was characteristic of all these patients. The age range for these patients was between 35 and 47, with a mean of 39.3 years. The duration of the illness was between 9 and 28 years, with a mean duration of 17 years. The patients had been hospitalized from 3 to 28 years, with an average of 14 years. The clinical data on the institutionalized patients are summarized in Table 2.

Bilateral testicular biopsies were performed on all patients, essentially according to the techniques of Charney[14] and Hotchkiss.[15] Biopsy specimens from the testes were fixed in

13. Blair, J. H.; Sniffen, R. C.; Cranswick, E. H.; Jaffe, W., and Kline, N. S.: The Question of Histopathological Changes in the Testes of Schizophrenics, J. Ment. Sc., to be published.

14. Charney, C. W.: Testicular Biopsy: Its Value in Male Sterility, J. A. M. A. **115**:1429, 1940.

15. Hotchkiss, R. S.: Fertility in Men: A Clinical Study of the Causes, Diagnosis and Treatment of Impaired Fertility in Men, Philadelphia, J. B. Lippincott Company, 1944, (*a*) pp. 169-173; (*b*) p. 14; (*c*) p. 16; (*d*) p. 33; (*e*) p. 27

Bouin's or Zenker's fluid. The fixed tissue was sectioned at 5 μ, and representative sections were stained with a variety of tissue stains, including iron-hematoxylin and eosin, Masson's trichrome stain, and Hotchkiss-McManus and aldehyde-fuchsin stains. Additional material was fixed routinely in neutral formalin for frozen-section study and was subjected to the following staining procedures for the demonstration of lipids: Sudan black B and Nile blue, Schultz test for cholesterol, Smith-Dietrich method, Schiff's reaction, and birefringence. Analyses of testicular morphology were thus based on both histological and histochemical data.

TABLE 1.—*Data on Age, Subtype, Duration of Illness, and Appetite for the Noninstitutionalized Patients with Schizophrenia*

Case	Age, Yr.	Type	Duration of Illness	Appetite
1	25	Paranoid	4 mo.	Poor for 4 wk., with 15 lb. loss of weight
2	20	Paranoid	2 mo.	Poor for 1 wk., with 10 lb. loss of weight
3	31	Paranoid	6 wk.	.....
4	22	Paranoid	3 mo.	.....
5	28	Paranoid	4 mo.	.....
6	20	Paranoid	8 mo.	.....
7	33	Paranoid	8 mo.	Variable, but no apparent loss of weight
8	22	Hebephrenic	4 yr.	Variable, but no apparent loss of weight
9	21	Catatonic	4 mo.	Poor for 2 wk.
10	20	Catatonic	18 mo.	.....
11	19	Catatonic	1 mo.	.....
12	39	Paranoid	4 mo.	.....
13	19	Paranoid	4 mo.	Poor for 2 wk.
14	27	Paranoid	5 mo.	Poor for 2 wk.
15	22	Simple	6 yr.	.....
16	27	Simple	10 yr.	.....

TABLE 2.—*Data on Age, Subtype, Duration of Illness, Duration of Hospitalization, and Appetite for the Institutionalized Patients with Schizophrenia*

Case	Age, Yr.	Type	Duration of Illness, Yr.	Duration of Institutionalization, Yr.	Appetite
17	47	Catatonic	28	28	Patient often refused to eat during first few years of illness
18	37	Catatonic	21	20	Often poor; feedings by gavage for prolonged periods
19	35	Catatonic	19	16	Periods in which patient did not eat, leading to 20 lb. loss of weight
20	37	Hebephrenic	15	11	.....
21	40	Hebephrenic	12	12	Often poor, with periods of loss of up to 20 lb. in weight
22	44	Paranoid	9	3	Periodically poor, with loss of weight up to 12 lb.
23	35	Simple	14	8	Poor, with loss of weight up to 12 lb.

NORMAL VARIATIONS OF TESTICULAR MORPHOLOGY

The testes ideally function in maintaining a satisfactory amount of germinal cell activity for fertility and enough Leydig cell activity for a normal sex hormone balance. Criteria for establishment of the degree of function are (1) an orderly pattern of spermatogenesis, (2) uniformity of tubular size, (3) minimal peritubular fibrosis, and (4) adequate Leydig cell function.[16]

16. (*a*) Nelson, W. O., and Heller, C. G.: Hyalinization of the Seminiferous Tubules Associated with Normal or Failing Leydig-Cell Function: Microscopic Picture in Testis and Associated Changes in Breast, J. Clin. Endocrinol. **5**:13, 1945. (*b*) Sniffen, R. C.: The Testis: I. The Normal Testis, Arch. Path. **50**:259, 1950. (*c*) Nelson, W. O.: Testicular Morphology in Eunuchoidal and Infertile Men, Fertil. & Steril. **1**:477, 1950; (*d*) Interpretation of Testicular Biopsy, J. A. M. A. **151**:449, 1953.

The human testis may be regarded as normal when there is evidence of a pattern of orderly and active spermatogenesis in at least 80% of the tubules, with mature spermatozoa in the majority of these tubules. As spermatogenesis apparently proceeds in waves of activity along the tubule, various cell types will predominate in the tubules at various levels. In the lumina are seen inconstant cell populations, made up of a few spermatozoa and spermatids and spermatocytes. Ordinarily, the maturing spermatozoa lie in the Sertoli syncytium, and few are free in the lumina, since once they are detached they are transported to the epididymis. There is little sloughing of immature cells in the normal testis.

The tubules should be uniform in size and show minimal peritubular fibrosis. With the advancement of peritubular fibrosis, the tubules become atrophic and reduced in size and show irregular configurations. The basement membrane of the tubules normally is a very thin, delicate structure composed of fine, homogeneous fibrils. The tunica propria, which surrounds the basement membrane, is composed of several lamellae of elastic and collagenous fibers, interspersed with fibroblasts. Simple fibrosis appears to be a normal aging process and involves primarily the tunica propria. With more advanced sclerosis, there is involvement of both the basement membrane and the tunica propria, with thickening of the latter, due to an increase of elastic fibers accompanied by some degree of hyalinization. This leads to a decline in tubular size and a somewhat woolly appearance. It is not uncommon to find that as many as 10 to 15% of the tubules may be involved in serious sclerosis with poor spermatogenesis, while the balance of the tubules show little or no sclerosis and a normal spermatogenic pattern. Such testes are regarded as being within the limits of normality.

The most important feature of the interstitial spaces is the Leydig cells. These are most difficult to evaluate, as the type and distribution may vary appreciably throughout the testis. The typical mature cells are characterized by large vesicular, usually eccentric, nuclei containing one or two nucleoli. Chromatic material is present in diffuse granular masses, usually about the periphery of the nucleus. Crystalloids, of varying sizes, and granules are characteristic features of the cytoplasm. The latter are believed to be closely related to the functional activity of the cell. Vacuoles are seen occasionally in various parts of the cell and probably are related to degenerative processes. Although cells of the type described above have been generally regarded as the functional form of the Leydig cell, there is reason to believe that the smaller, granular type of cells is a more active producer of hormones than the larger, somewhat vacuolated elements. However, the standards of evaluating degrees of endocrine activity of the Leydig cells in the testes of noneunuchoidal men have not been very well defined.

DATA

All morphological examinations of the biopsy specimens from the two testes were based on the criteria for the normal variation of testicular histology described above. Table 3 summarizes the histological findings in the testes of the noninstitutionalized patients. In 9 of the 16 patients in this group the structure of both testes was considered well within the normal limits of variation. These minor variations were in spermatogenesis, tubular size, and peritubular fibrosis. In two additional patients the testes morphology was considered characterized as normal on the basis

of a normal histological appearance of one testis, even though the other testis was considered abnormal. Figure 1 illustrates the normal histological characteristics of the testes for this group of 11 patients.

Of the 16 patients, the testes of 2 were considered to be characterized by sufficient abnormalities of spermatogenesis, irregularity of tubular size, and moderate peritubular fibrosis to be judged as slightly abnormal. Figure 2 illustrates representative histological deviations in the testes of these two patients.

TABLE 3.—*Summary of the Histological Structure of Testes in the Noninstitutionalized Patients**

Case	Spermatogenesis	Tubular Size	Peritubular Fibrosis	Leydig Cells	Impression of Testes Morphology
1	Good	Regular	Right: mild to moderate, 15% Left: none	Normal	Normal
2	Mild sloughing	Slightly reduced	Right: 10% Left: 20%	Slightly reduced in number	Normal
3	Mild sloughing	Regular	Mild to moderate in 40%	Normal	Normal
4	Good	Regular	Right: 10% Left: 5%	Normal	Normal
5	Good	Regular	Moderate in 25%	Normal	Normal
6	Moderate hypoplasia and sloughing	Slightly reduced	Right: minimal Left: 20%	Normal	Moderately abnormal
7	Normal	Regular	None	Normal	Normal
8	Right: moderate sloughing Left: normal	Right: irregular Left: regular	Right: 25% Left: 5%	Right: reduced Left: normal	Right: slightly abnormal Left: normal
9	Right: severe sloughing Left: not biopsied	Right: reduced	Right: 40%	Right: poor	Right: definitely abnormal
10	Hypoplasia	Reduced	Right: 20% Left: 30%	Normal	Moderately abnormal
11	Moderate sloughing	Regular	Minimal	Normal	Normal
12	Moderate hypoplasia	Irregular	Right: 15% Left: 25%	Normal	Slightly abnormal
13	Mild hypoplasia	Regular	Minimal	Normal	Probably normal for age (18 yr.)
14	Moderate sloughing	Irregular	40%; moderate to severe	Excessive no. of vacuolated cells	Slightly abnormal
15	Right: hypoplasia Left: good	Right: irregular Left: regular	Right: severe Left: minimal	Right: reduced numbers Left: normal	Right: moderately abnormal Left: normal
16	Good	Regular	10%	Normal	Normal

* The findings apply to both testes unless otherwise stated.

For the three remaining patients in the group of noninstitutionalized patients the testicular histology revealed a severer degree of abnormality. The disturbances of spermatogenesis, reduction and irregularity in tubular size, and degree of peritubular fibrosis were very prominent. Figure 3 illustrates these findings.

Table 4 summarizes the testicular histology for the seven institutionalized patients. Histological examination of the testes of three of these patients revealed variations in spermatogenesis, tubular size, and peritubular fibrosis which were considered to be within normal limits. Four of the patients, however, had a moderate degree of abnormality, as indicated by the degree of sloughing and hypoplasia of spermatogenesis, the reduction and irregularity of tubular size, and the degree of peritubular fibrosis. Figures 1 and 3 serve to illustrate the normal and moderately abnormal testicular histology which characterized this group.

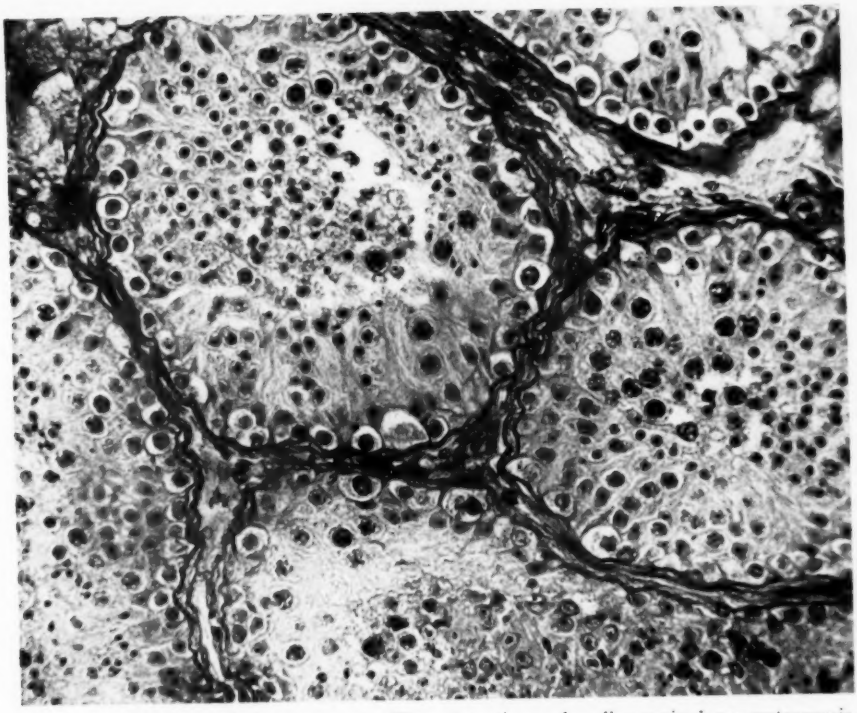

Fig. 1.—Normal testicular structure. There is active and well-organized spermatogenesis throughout; the lumina are open, and the tubular size is regular. There are both minimal sloughing and peritubular fibrosis. × 300.

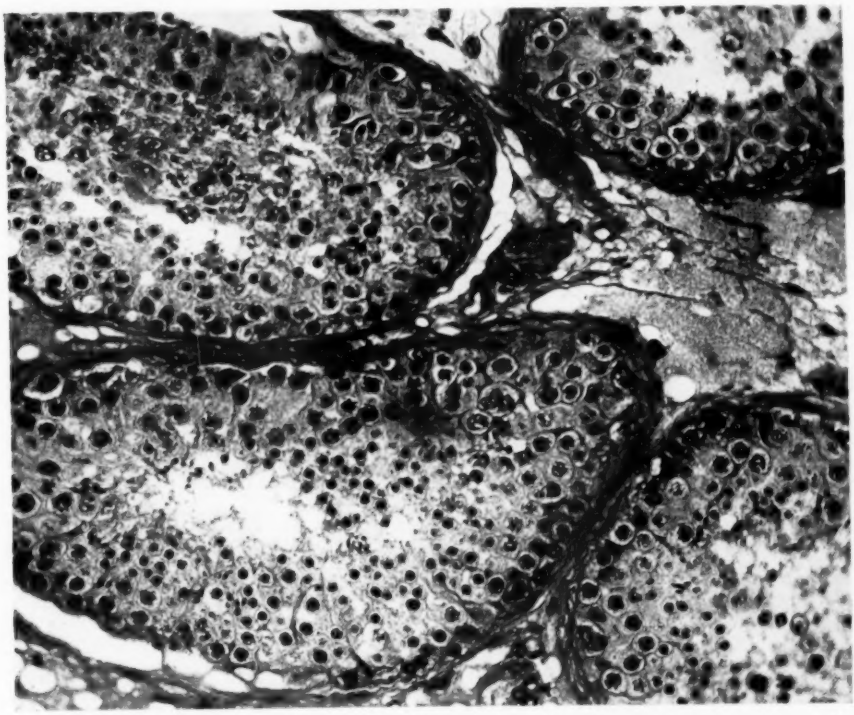

Fig. 2.—Slightly abnormal testicular structure. There is mild hypoplasia of spermatogenesis with moderate sloughing of the cellular elements in 25 to 30% of the tubules, but an adequate number of spermatozoa for fertility are being formed. Mild to moderate peritubular fibrosis is present, involving 20 to 25% of the tubules. × 300.

On the basis of the histological examination of the testes for the entire group of 23 patients, the Leydig cells were classified as normal in 16 patients, as slightly reduced in number in 3, as excessively vacuolated in 2, and as poor in 2.

Table 5 indicates the relation of testicular morphology to the schizophrenic subgroups for both the noninstitutionalized and the institutionalized group of patients. In the noninstitutionalized group, normal testicular histology characterized 7 of 10 patients who were paranoid, 1 of 3 who were catatonic, 1 who was hebephrenic, and 2 who had simple schizophrenia. Two paranoid patients were

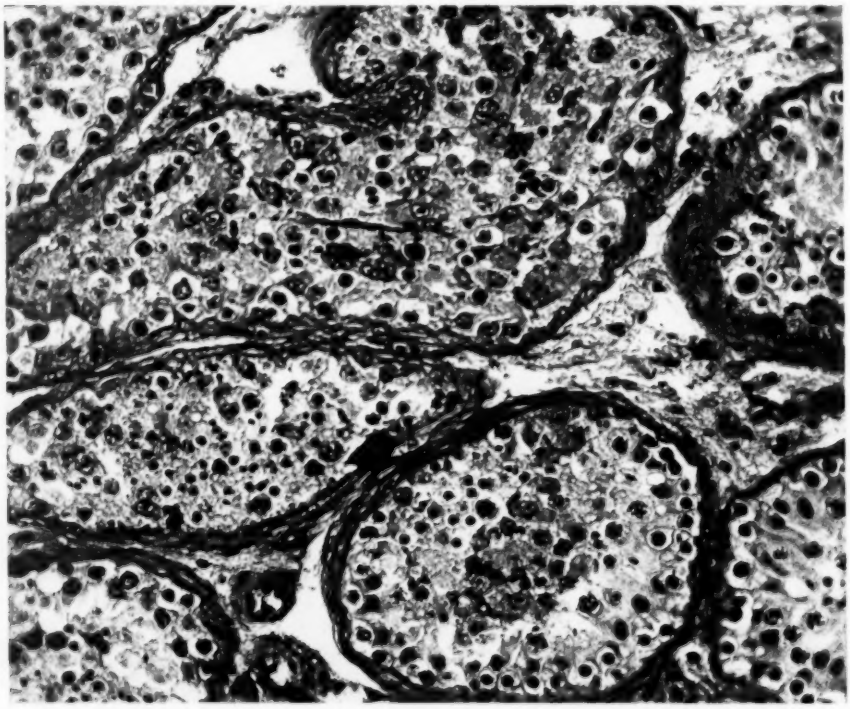

Fig. 3.—Moderately abnormal testicular structure. There is hypoplastic spermatogenesis with definite sloughing of the cellular elements. There is spermatogenic disorganization, and mature sperm are present in reduced numbers. The tubules are reduced in size and show moderate to severe peritubular fibrosis. × 300.

considered to have slightly abnormal, and 1 moderately abnormal, testicular structure. A moderate degree of abnormality characterized the testes of two of the three catatonic patients.

In the chronically ill, institutionalized group, one paranoid and three catatonic patients had a moderate degree of testicular abnormality, while the one patient with simple schizophrenia and the two with hebephrenic schizophrenia were regarded as having normal testicular structure.

Although the number of patients in each subgroup is small, when the noninstitutionalized and the institutionalized group are combined, the data suggest that

TABLE 4.—*Summary of the Histological Structure of the Testes in the Institutionalized Patients**

Case No.	Spermatogenesis	Tubular Size	Peritubular Fibrosis	Leydig Cells	Impression of Testes Morphology
17	Moderate hypoplasia and sloughing	Reduced	15-20%	Reduced numbers, atypical	Moderately abnormal
18	Mild hypoplasia in 40%; partial germinal cell arrest	Regular	Minimal	Normal	Moderately abnormal
19	Moderate hypoplasia and sloughing	Reduced	Mild to moderate in all; severe to complete in 25-30% on left and 15-20% on right	Poor	Moderately abnormal
20	Right: fairly normal Left: normal	Right: reduced Left: normal	Right: severe to complete in 25-30% Left: moderate to severe in 10%	Normal Normal	Right: slightly abnormal Left: normal
21	Hypoplasia in 20%; others normal	Normal	Severe in 5-10%	Slightly reduced	Normal
22	Moderate hypoplasia and sloughing	Reduced	Mild to moderate in 40%; severe in 20%	Normal	Moderately abnormal
23	Mild disorganization and sloughing	Regular	Mild to moderate in 30%; severe in 10-15%	Slightly reduced	Normal

* The findings apply to both testes unless otherwise stated.

TABLE 5.—*Relation of Testes Morphology to Schizophrenia*

Testicular Morphology	Subclassification				
	Paranoid	Catatonic	Hebephrenic	Simple	Total
Noninstitutionalized Patients					
Normal	7	1	1	2	11
Slight abnormality	2	..	..	..	2
Moderate abnormality	1	2	..	..	3
Total	10	3	1	2	16
Institutionalized Patients					
Normal	..	..	2	1	3
Moderate abnormality	1	3	..	..	4
Total	1	3	2	1	7
All Patients					
Normal	7	1	3	3	14
Slight abnormality	2	..	..	..	2
Moderate abnormality	2	5	..	..	7
Total	11	6	3	3	23
Leydig Cells					
Normal	9	3	2	2	16
Slightly reduced	1	..	1	1	3
Excessively vacuolated	1	1	..	..	2
Poor	..	2	..	..	2
Total	11	6	3	3	23

histological variations within normal limits are characteristic of the testes of patients in the subgroups of paranoid, hebephrenic, and simple schizophrenia. This is particularly true if a slight degree of deviation of testicular structure is not considered as of great significance. Only patients with catatonia were characterized by an abnormality of the testicular morphology, for five of the six patients in this group revealed a moderate degree of abnormality. This observation is further substantiated by the appearance of the Leydig cells, since these, too, showed defects.

Table 6 presents the relation of duration of the illness to the testicular morphology. Five of the seven patients with a moderate degree of abnormality of the testicular histology had been chronically ill. On the other hand, other patients who had been ill for as long a time had normal testes. In contrast, only 2 of 12 patients ill for one year or less had a moderate degree of testicular abnormality. The data suggest that duration of illness may be related to testicular morphology but that

TABLE 6.—*Relation of Duration of Illness to Testicular Morphology*

	Duration of Illness				
Testicular Morphology	6 Mo. or Less	7 Mo.-1 Yr.	1-5 Yr.	Over 5 Yr.	Total
Normal	7	1	1	5	14
Slightly abnormal	2	..	..	..	2
Moderately abnormal	1	1	1	4	7
Total	10	2	2	9	23

TABLE 7.—*Relation of Disturbance in Appetite to Testicular Morphology*

	Appetite			
Testicular Morphology	Normal	Capricious	With Severe Weight Loss	Total
Normal	7	3	4	14
Slightly abnormal	2	..	..	2
Moderately abnormal	1	3	3	7
Total	10	6	7	23

some other factor or factors associated with length of illness are also responsible. These might relate to the schizophrenic process itself or to the process of institutional care of chronic patients.

Table 7 presents the relation of disturbance of appetite to testicular morphology. Nutritional deficiency, which frequently is a concomitant of the schizophrenic illness, has also been implicated as one of the prominent causes of testicular abnormality.[15b] Six of the seven patients with a moderate testicular abnormality had a history of periods of disturbance in their nutritional status. On the other hand, a history of periods of similar nutritional deficiency characterized some of the patients with normal testes. In contrast, only 1 of the 10 patients with no history of an appetite disturbance had testes characterized by a moderate degree of abnormality. The implication, then, is that nutritional disturbances may be significant in the development of testicular abnormality in patients with schizophrenia, although the data do not exclude the operation of other factors.

COMMENT

This study concerned the testicular morphology in 11 patients subclassified as paranoid, 6 as catatonic, 3 as hebephrenic and 3 as having simple schizophrenia, a total of 23 patients. The histological structure of the testes was considered within the normal limits of variation for all these patients except for four in the paranoid group and five in the catatonic group. The degree of abnormality of the testicular structure was slight for two of the four patients in the paranoid group. The testes of the other two paranoid patients and of the five catatonic patients were characterized by a moderate degree of abnormality, which included for three of the catatonic group a reduction in Leydig cell activity.

These results suggest that abnormality of testicular structure is not a characteristic of the schizophrenic process, with the possible exception of catatonia. These findings, therefore, do not confirm those of Hemphill, Reiss, and Taylor.[11a] Furthermore, none of the testicular conditions encountered in this series of patients were in any way unique. They have been seen and described many times in the testes of men whose sole complaint was infertility.[16c,d] The extensive hyalination of the basement membranes reported by Hemphill, Reiss, and Taylor [11a] was not observed. However, its occurrence would not be surprising, since it is not uncommon in men without mental disturbances.

Since a moderate amount of atrophy did occur in the testes of some of the patients with schizophrenia, and since the evidence suggests that this atrophy is not part of the histopathology of the schizophrenic process, the question is raised as to whether or not the data suggest any concomitant factors that may be responsible for the atrophy. It has been reported that testicular function is influenced by such factors as heredity, age, nutrition, temperature, infections, neoplasms, obstructions, circulation, irradiation, pressure, and endocrine and constitutional states.[15b] Temperature, neoplasms, obstructions, circulation, irradiation, and pressure probably do not play a role in patients with schizophrenia. Studies on men have provided little evidence to permit any conclusions concerning the relation of heredity to abnormalities of testicular function [15c] except in certain characteristic hypogonadal syndromes, such as that of Klinefelter.[17] Spermatogenesis decreases with age, but Engle [18] reported abundant spermatozoa in the testes and ducts of more than half of a group of men past 70. Age should not play an important role in the schizophrenic patients examined in the present study. Certain emotional states, such as fatigue and anxiety, very possibly may play a role in human infertility. No well-controlled studies have been made, however, and this factor, although a possibility in catatonia, cannot be evaluated by our data. Testicular abnormalities may occur as a result of generalized infections.[15e] Although patients with chronic schizophrenia are prone to the development of infectious illnesses, none of the patients in this series, as far as is known, had had severe or chronic infectious diseases.

17. Klinefelter, H. F., Jr.; Reifenstein, E. C., Jr., and Albright, F.: Syndrome Characterized by Gynecomastia, Aspermatogenesis Without A-leydigism, and Increased Excretion of Follicle-Stimulating Hormone, J. Clin. Endocrinol. **2**:615, 1942.

18. Engle, E. T.: Relation of the Anterior Pituitary Gland to Problems of Puberty, A. Res. Nerv. & Ment. Dis. Proc. **17**:298, 1936.

The testes are closely related to other endocrine organs, particularly the anterior lobe of the pituitary, which controls both spermatogenesis and Leydig cell function through the release of gonadotropin. The follicle-stimulating fraction influences spermatogenesis, and the luteinizing fraction influences release of testosterone by its action on the Leydig cells.[19] Hemphill and Reiss [12] believed their studies indicated that the testicular atrophy reported in schizophrenia was probably related to inadequate gonadotropin control, but their data are not convincing and have not been confirmed in this study. Schizophrenia has often been believed to involve endocrine systems, but no specific evidence for this has been provided.[20]

Nutrition is closely related to testicular function, and subclinical states of nutritive failure hold great interest in terms of testicular morphology. In some animals, at least, adequate quantities of both vitamin A and vitamin E, as well as proteins and minerals, are required for normal testicular function.[21] Klatskin and associates,[22] in a study of gynecomastia due to malnutrition in American prisoners of war, found evidence of testicular atrophy in one-third of the patients studied. Oligospermia was present in the released prisoners both with and without gynecomastia. The authors believe that malnutrition depresses testicular function, either directly or by interfering with pituitary function. The data reported in this study suggest that nutritional deficiency is a factor related to testicular atrophy. It is likely that in certain patients periods of selective malnutrition have led to irreversible changes in the testes. Later, the nutritional state may be improved, but without concomitant improvement in testicular function. As was true of malnourished prisoners of war, not all patients would show the same degree of testicular damage or lack of subsequent improvement.

Clinical experience would indicate that the catatonic patients as a group are more liable to have periods of severe disturbance of appetite and nutritional intake than are patients in the other schizophrenic subgroups. Length of hospitalization and duration of illness are factors to be considered in relation to nutritive failure in patients with schizophrenia, since the longer the illness and period of hospitalization, the more liable are selective nutritional deficiencies to occur. The data reported in this study suggest that chronicity of illness is a factor related to the atrophic changes that were observed in some of our patients.

SUMMARY AND CONCLUSIONS

An evaluation of testicular morphology in schizophrenia has been made through the utilization of bilateral testicular biopsies in 23 patients with typical schizophrenia. Of these, 16 were designated as noninstitutionalized, since they were

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22. Klatskin, G.; Salter, W. T., and Humm, F. D.: Gynecomastia Due to Malnutrition: I. Clinical Studies, Am. J. M. Sc. **213**:19, 1947.

studied shortly after their first hospitalization, and the remaining 7, as institutionalized, since they had been hospitalized for a number of years. Eleven patients were in the paranoid subgroup. In four of these the testicular histology deviated from the normal, but in two of the four the degree of abnormality was regarded as slight. The three patients in the subgroup of simple schizophrenia and the three patients in the subgroup of hebephrenic schizophrenia had normal testes. Only in the subgroup of the catatonic type, in which the testes of five of the six patients showed significant departures from the normal, was there a suggestion of a relationship between schizophrenia and testicular structure.

The observed testicular defects were not unique for patients with schizophrenia but were similar to those that have been observed in many men whose only complaint was infertility.

The data suggest that chronicity of illness and nutritional deficiency are related to testicular atrophy. It may be hypothesized that the longer the duration of illness, the greater the chance for subclinical nutritive failure to occur, particularly in patients with catatonia, and to be reflected in the testicular morphology.

It may be concluded that specific abnormalities of testicular structure and function do not characterize schizophrenia.

VENTRICULAR DISPLACEMENT AND ELECTROENCEPHALOGRAPHIC FOCUS IN MULTIPLE SCLEROSIS

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PITTSBURGH

MULTIPLE sclerosis often simulates a brain tumor, but the history and the impossibility of explaining the symptoms and signs on the basis of a single lesion usually establish the diagnosis. It is known that electroencephalograms show a tendency to slow focal activity in this disease, but the relatively few reports of air studies in multiple sclerosis have revealed only minor changes, all described as being due to diffuse or patchy cerebral atrophy, with secondary minor enlargement of the ventricular system.

REPORT OF A CASE

The present case illustrates a ventricular displacement in multiple sclerosis entirely compatible with the diagnosis of a brain tumor.

D. R., an automobile mechanic aged 29, was admitted to the Veterans Administration Hospital in Pittsburgh, on Sept. 9, 1952, with the complaint of paralysis of the left side, dizziness, and headaches. Nine years before he had joined the Air Corps and had completed 31 war missions as a gunner. Since that time his hearing had been impaired bilaterally. After a period of limited duty, on account of operational fatigue, he was discharged in 1945 with a diagnosis of anxiety neurosis. After working one year as a coal miner, he enrolled in a school for automobile mechanics. About 1947 he first noticed spells of mild dizziness and "funny feelings" in his hands. He became irritable and worried a great deal about the peculiar sensations in his hands; he found difficulty in getting and holding a job, which he blamed partly on his impaired hearing. He tired easily, and occasionally he noticed unsteadiness, slurred speech, and clumsiness of one limb or the other. In 1951 he had several episodes of sudden severe dizziness with blurred vision and a feeling of faintness; one day in October the right hand became almost paralyzed and the feet paretic. The paresis of the lower extremities subsided within a few days, but it took four months for the right hand to become strong again. In December, 1951, there was another episode of temporary paresis of the right hand. Various visual, motor, and sensory symptoms continued to occur for short periods, with remissions and exacerbations. In the first week of October, 1952, he became violently dizzy; paralysis of the left extremities developed within a day, together with diffuse headache, nausea, and vomiting.

The patient had had more or less regular medical attention, and the records accompanying him on admission mentioned several episodes of hysterical paralysis, rages, and attacks of unconsciousness; the referral diagnosis was "hysterical panic reaction." He undoubtedly had displayed considerable emotional instability. A careful check of the history pointed to some epileptiform attacks but no grand mal seizures. Several short episodes of dizziness, unsteadiness, and fatigue

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had occurred and had been so severe that he had appeared helpless during them. They were occasionally combined with such slurring and impairment of speech as to render the patient unable to make himself understood for hours.

Examination.—The patient appeared acutely ill; he was emotional and was unwilling to move his head because of dizziness and generalized headache. He was alert; his sensorium was clear, his speech slurred, and his hearing slightly impaired bilaterally; the eyegrounds showed temporal pallor, and there were horizontal nystagmus bilaterally, paralysis and hypesthesia of the left extremities, increased deep reflexes, especially on the left, a Babinski sign on the left, and absence of abdominal reflexes. The spinal fluid was clear and colorless and under a pressure of 210 mm., with 2 white cells per cubic millimeter and 68 mg. of protein per 100 cc.; the colloidal gold curve was flat. The electroencephalogram showed a pronounced slow-wave focus in the right frontoparietal area (Fig. 1). The findings in other laboratory studies and in roentgenograms of the skull and chest were within normal limits.

Course.—A second spinal puncture, a few days later, showed a pressure of 150 mm. A pneumoencephalogram revealed displacement of the lateral ventricles to the left and a pronounced

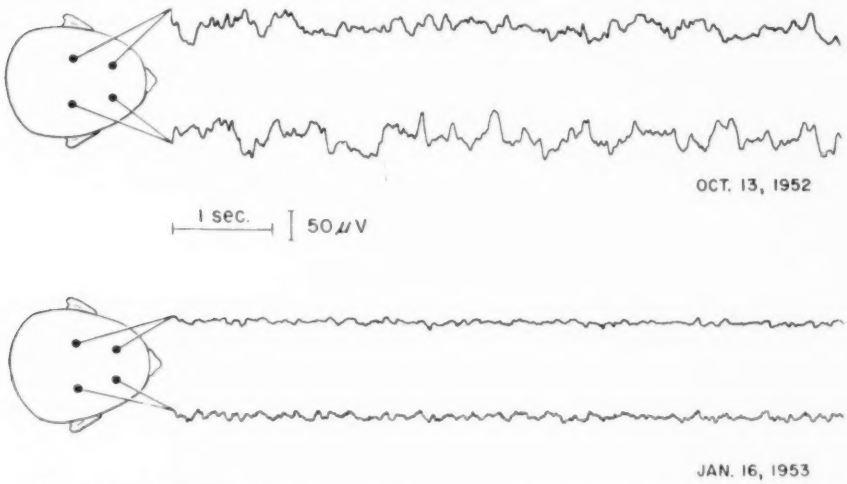

Fig. 1.—An electroencephalogram taken Oct. 13, 1952, shows a slow-wave focus in the right frontoparietal area. A new tracing, taken Jan. 16, 1953, was within normal limits.

distortion of the midportion of the right lateral ventricle, with some compression of the right temporal horn, as though there were a tumor centering in the right Rolandic area (Fig. 2). After two to three weeks the patient showed rapid improvement; his dizziness, nausea, and headache diminished. Some function returned in the left extremities; he began to sit up and to move around a little, and ataxia of the left arm could then be demonstrated. He was given a three-week furlough and, because of further improvement, a second furlough. On Jan. 16, 1953, another pneumoencephalogram and electroencephalogram both revealed a condition within normal limits except for slight symmetrical dilatation of the ventricles (Fig. 3). At that time the nystagmus had subsided; there was excellent strength in both hands, but the left hand still had some ataxia, and he said it did "not feel quite right." He had already started to do light work. Some of his contentment may have been on the basis of euphoria. When seen again, eight months after the first air studies, he still complained that his hands, particularly the left, periodically felt numb and that one leg, this time the right, had "become kind of weak the last three or four months." He was getting along rather well, however; he had no pain and had been working as a garage man since his discharge from the hospital. A slow, slightly slurred speech; mild intention tremor; noticeable ataxia of the left hand; increased deep reflexes,

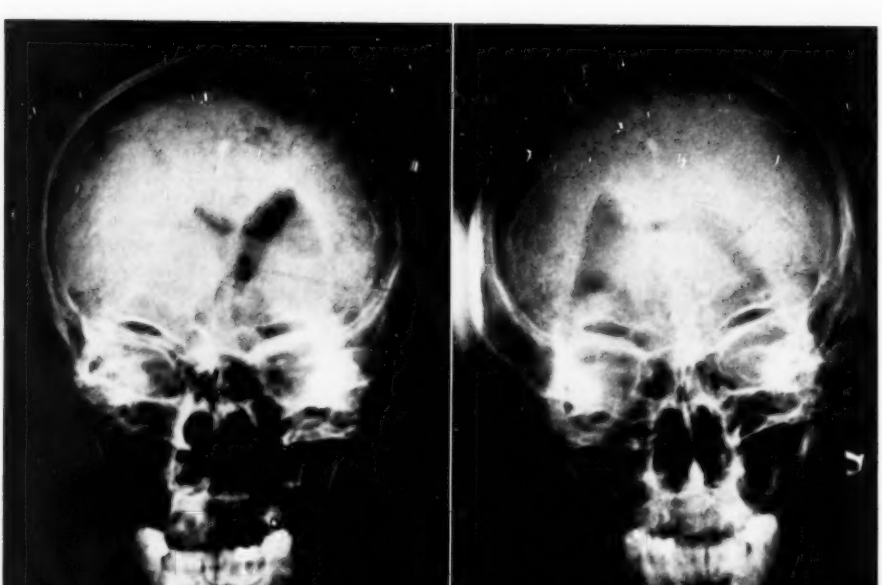

Fig. 2.—Pneumoencephalograms, taken Oct. 27, 1952, show a displacement of the lateral and third ventricles to the left compatible with a diagnosis of tumor of the right frontoparietal area.

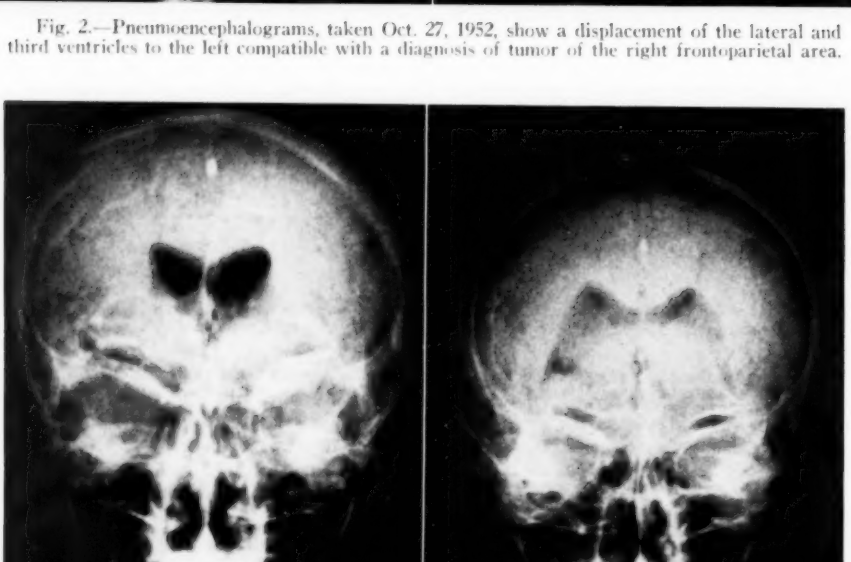

Fig. 3.—Pneumoencephalograms, taken Jan. 15, 1953, show essentially normal ventricles except for slight dilatation.

especially on the left; absence of abdominal reflexes, and some paresis of the right foot were the essential findings. There was no paresis of the left extremities. The spinal fluid, under a pressure of 150 mm., had 3 white cells per cubic millimeter and 30 mg. of protein per 100 cc., and the colloidal gold curve was normal. Two months later his condition was essentially unchanged, and he was working regularly.

COMMENT

A diagnosis of multiple sclerosis was made upon the patient's admission. The emotional outbursts seemed a logical sequel to the unexplained, frightening, and disabling symptoms. It was the history of convulsions, the initially increased spinal fluid pressure, and a slow-wave focus in the electroencephalogram that prompted the air studies.

Convulsions in multiple sclerosis are not unknown. A recent review of the literature by Williams and associates [1] included the report of four cases with convulsions among their own "300 to 400 cases" of multiple sclerosis. The frequency of abnormal electroencephalograms has been debated. Gibbs and Gibbs [2] found "no significant changes," and Freeman [3] noted that "the electroencephalogram of multiple sclerosis is substantially normal." On the other hand, Hoefer and Guttman,[4] Jasper and associates,[5] and Williams and associates [1] noted frequent focal changes and pointed out that in acute exacerbations the electroencephalograms were noticeably abnormal in about two-thirds of the cases. The electroencephalogram of multiple sclerosis shows nothing diagnostic; the common abnormalities that have been described are mild, diffuse dysrhythmia with minor focal wave activities. The location of the slow waves usually does not correlate well with the clinical picture. It is uncommon to find a slow-wave focus as prominent as that in this case.

The question then arose: Could the patient have a brain tumor in addition to his multiple sclerosis? Such a situation was described in 1949 by Munch-Petersen [6] in a woman who had had multiple sclerosis for nine years, then rather suddenly became comatose and died one day later. Autopsy showed both *sclérose en plaques* and an ependymoma of the midportion of one cerebral hemisphere, extending into the mesencephalon and pons. Carter and associates [7] reported that in 2 of 46 cases of multiple sclerosis in which autopsy was performed at the Montefiore Hospital from 1909 to 1948 death was from cerebral neoplasm.

There is little in the literature on air studies in multiple sclerosis. Hoefer and Guttman [4] noted that in their material of 127 cases of multiple sclerosis, "pneumo-

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5. Jasper, H.; Bickford, R., and Magnus, O.: The Electro-Encephalogram in Multiple Sclerosis, A. Res. Nerv. & Ment. Dis., Proc. **28**:421-427, 1950.

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7. Carter, S.; Sciarra, D., and Merritt, H. H.: The Course of Multiple Sclerosis as Determined by Autopsy Proven Cases, A. Res. Nerv. & Ment. Dis., Proc. **28**:471-511, 1950.

encephalograms were reported in only 11 cases. All were normal except for the 2 in the abnormal EEG group." In the discussion on this paper, Putnam [8] stated that he had used roentgenencephalography "fairly frequently" in the differential diagnosis of certain clinical forms of multiple sclerosis. The only actual reports on pneumoencephalographic studies in cases of multiple sclerosis are those by Scott [9] (6 cases), Freeman [3] and Freeman and Cohn [10] (15 cases), Koschewnikoff and Fraenkel [11] (1 case), Vercelli [12] (8 cases), and Williams and associates [1] (3 cases). These air studies have either presented a normal condition or shown air pockets and stellate shadows, mostly located over the frontal lobes and Sylvian fissures. In some instances the lateral ventricles were asymmetrically dilated to a slight degree. These changes were apparently caused by a shrinkage of cerebral substance and were fairly well correlated with changes at autopsy. Carter and associates [7] reproduced a pneumoencephalogram showing "ventricular dilatation and cortical atrophy" in a case of multiple sclerosis, without further description of the case. Freeman [3] wrote: "There are no focal wanderings of the ventricles, seen so often in traumatic atrophies." None of the authors described any shift or distortion of the ventricles that simulated the roentgenologic signs of a cerebral tumor.

The ventricular deformity in the first air studies in the present case extended not only into the frontal and parietal lobes but also, to a less degree, into the temporal lobe, and appeared to be caused either by a space-occupying lesion or by a localized swelling of the brain itself centering in the area of the right Rolandic fissure. If a cerebral tumor had been responsible for the encephalographic changes, a large hemorrhage in that tumor could have explained the rather sudden paralysis of the entire left side. If such a hemorrhage had been present in that area, the patient should have been drowsy. This man, however, was alert; his neck was not stiff, and the cerebrospinal fluid was clear and colorless and, on the second tap, under normal pressure. A tumor gradually destroying the brain substance would hardly have given such an extensive paralysis within one day; a tumor diffusely infiltrating partially functioning brain substance would hardly have caused complete paralysis of the left extremities and distorted the parietotemporal area to the extent the air studies indicated without producing a cut in the visual fields or a persistent increase of intracranial pressure. Therefore it was assumed that the ventricular shift was due to a localized swelling of the brain caused by an acute sclerotic plaque, and not to a tumor. An exploratory craniotomy was not performed.

The subsequent clinical course and the essentially normal pneumoencephalogram and electroencephalogram taken 10 weeks after the first ones confirmed the impression that the condition was multiple sclerosis alone, and not multiple sclerosis combined with a brain tumor. The thrombotic and parenchymatous changes in a large

8. Putnam, T. J.: In discussion on Hoefer and Guttman.[4]

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10. Freeman, W., and Cohn, R.: Electroencephalographic and Pneumoencephalographic Studies of Multiple Sclerosis, Arch. Neurol. & Psychiat. **53**:246, 1945.

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plaque apparently led to such edema in the vicinity of the motor strip that not only total loss of function of the opposite extremities but also focal changes in the electroencephalogram and a grossly abnormal pneumoencephalogram were produced. These findings indicative of a "pseudotumor" gradually disappeared, and normality was again approached when the edema had subsided. The acute lesion of multiple sclerosis in the frontoparietal area was probably not followed by any extensive necrosis, for if it had, the return of function would not have been so prompt.

Perivascular and pericellular collections of fluid are found around fresh plaques, but in the present case the local edema was apparently excessive, leading to such marked ventricular distortion, typical of tumor, that a craniotomy would have been indicated had it not been that this "tumor deformity" did not seem to fit in well with the clinical course and the symptoms and signs presented by the patient. It was surprising to find these marked electroencephalographic and ventricular abnormalities in multiple sclerosis and to see them disappear within a few weeks. The follow-up studies have substantiated the diagnosis on admission. It would seem, therefore, that to the pneumoencephalographic abnormalities that are known to occur in multiple sclerosis should be added a temporary ventricular displacement simulating that caused by brain tumor.

SUMMARY

Several reports of rather mild electroencephalographic abnormalities in multiple sclerosis were found in the literature. Few pneumoencephalographic studies have been published, and the only variations from normal that they have shown are those which followed atrophy of the brain. In this report it is demonstrated that a ventricular displacement, simulating that caused by a brain tumor, can also occur in multiple sclerosis. Both the ventricular distortion and the electroencephalographic focus of slow waves in the case presented disappeared within three months, when the acute symptoms had subsided.

CEREBRAL CIRCULATION AND METABOLISM IN MULTIPLE SCLEROSIS

Correlative Observations by Electroencephalography and Psychodiagnostic Testing

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THE ETIOLOGY and pathologic physiology of multiple sclerosis have remained obscure despite many excellent clinical and pathologic observations. Hypotheses which incriminate vascular spasm and venular thrombosis as factors mechanically responsible for the lesions of multiple sclerosis have incited considerable clinical investigation [1] and have provided the main basis for therapy of acute stages of the disease, namely, the use of so-called cerebral vasodilator drugs and drugs to inhibit formation of vascular thrombi.[2] One of the purposes of the present study, therefore, was to measure cerebral blood flow and metabolism in patients in various stages of multiple sclerosis in an effort to detect the possible presence of alterations in cerebral circulation and metabolism which might presumably be produced by vascular spasm or clotting. Simultaneously, it was hoped to determine whether the known pathological lesions in the brain in multiple sclerosis, whatever their cause, result in measurable alterations in cerebral blood flow, oxygen or glucose consumption, or vascular resistance, and at what stages in the illness such changes, if any, occurred.

Since multiple sclerosis is known to produce clinical changes in mental pattern, electroencephalographic tracings and psychodiagnostic tests were also performed on these patients, and an effort was made to correlate the results of these studies with the clinical severity of the disease and the measured cerebral circulatory and metabolic functions.

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MATERIAL AND METHODS

Twenty patients with proved multiple sclerosis in various stages of exacerbation and remission were included in this study: None of the subjects had intercurrent illnesses at the time of the study, and all were in a good state of nutrition. A modification[3] of the original nitrous oxide procedure[4] was used to measure cerebral blood flow. The patients were all studied in the fasting state. After the initial blood flow determination, nine of the subjects inhaled a mixture of 5% carbon dioxide and 95% oxygen for five minutes, at which time blood samples for oxygen determinations were drawn from the artery and the bulb of the internal jugular vein for measurement of the arterial-cerebral venous oxygen difference. These values were used as an indirect measurement of cerebral blood flow, since it has been shown that inhalation of such a gas mixture does not alter cerebral oxygen consumption.[5] After the blood flow measurements, 12 of the patients were taken directly for electroencephalography. After a rest period of one hour for lunch, the same 12 patients were taken for psychodiagnostic testing.

Blood oxygen determinations were done by the spectrophotometric technique of Hickam and Frayser.[6] Blood samples for oxygen determination were drawn before and after each blood flow measurement, and the average was used as the final value for the arterial-cerebral venous oxygen difference. Arterial and venous oxygen tensions were estimated from the pH and the percentage of oxyhemoglobin saturation, using the dissociation curves of Dill. The values for oxygen tension when oxyhemoglobin saturation was above 90% were obtained from a chart of interpolated values, using Dill's figures, and represent only an estimation. Carbon dioxide content of whole blood was measured by the method described by Peters and Van Slyke,[7] and carbon dioxide tension was estimated from the nomograms of Peters and Van Slyke.[7] The pH of whole blood was measured with the glass electrode of a Cambridge Model R pH meter at 34 C. and corrected to 38 C. by Rosenthal's factor.[8]

Blood glucose content was measured by the sodium thiosulfate titration method of Somogyi.[9] Arterial pressure measurements were made by the auscultatory method every two minutes during the procedure, with the arm held at heart level. Mean pressures were calculated from the formula

$$\text{MP} = \text{diastolic pressure} + \tfrac{1}{3} \text{ pulse pressure}$$

The electroencephalograms were recorded with a 6-channel Grass (Model III) electroencephalograph. Ten electrodes were employed, being distributed bilaterally over the frontal, anterior temporal, temporal, central, and occipital areas. Both bipolar and monopolar recordings were made, the ears serving as reference electrodes in the latter. Though the impossibility of quantitating electroencephalographic results is recognized, for the purpose of this correlative study, a numerical scale was established as a rough standard:

0 indicates no significant fast, slow, asymmetric, or paroxysmal activity; 1, diffuse mildly slow or mildly fast activity; 2, mildly slow or fast activity plus focal signs; 3, diffuse moderately slow

3. Scheinberg, P., and Stead, E. A., Jr.: The Cerebral Blood Flow in Male Subjects as Measured by the Nitrous Oxide Technique: Normal Values for Blood Flow, Oxygen Utilization, Glucose Utilization, and Peripheral Resistance, with Observations on the Effect of Tilting and Anxiety, J. Clin. Invest. **28**:1163, 1949.

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TABLE 1.—*Clinical and Electroencephalographic Data and Results of Rorschach Tests in Patients with Multiple Sclerosis*

Patient	Age, Yr.	Clinical Data	Clinical Scale	EEG	EEG Scale	Rorschach Ink-Blot Test
W. H.	33	Mild exacerbation; first attack 2 yr. ago Euphoria; diplopia; nystagmus	1	.....	..	.....
C. S.	51	No recent changes; duration 15 yr. Spastic quadriparesis; no cranial nerve or sensory involvement; questionable cerebellar tract involvement; no euphoria; memory good	4	.....	..	.....
M. W.	30	Duration 9 yr.; recent progression Spastic paraplegia; cord bladder; cerebellar ataxia in upper extremities; memory, concentration, and judgment poor	5	.....	..	.....
P. G.	47	Duration 5 yr.; no definite remissions; no recent changes Spastic monoparesis; cerebellar ataxia; optic atrophy; posterior column involvement; memory and judgment affected	2	.....	..	.....
V. C.	39	Duration 7 yr.; recent exacerbation Spastic paraparesis; cerebellar ataxia; optic atrophy; nystagmus; posterior column involvement; memory and judgment impaired	3	.....	..	.....
E. McD.	37	Duration 9 yr.; no recent exacerbation Nystagmus; pyramidal tract and cerebellar signs on left; no impairment of memory or judgment	2	.....	..	.....
C. W.	32	Duration 6 yr.; recent exacerbation Optic atrophy, O. D.; bilateral pyramidal tract, cerebellar, and posterior column involvement; memory, judgment, and concentration grossly impaired	2	.....	..	.....
W. S.	41	Duration 10 yr.; no recent exacerbation Spastic paraparesis, nystagmus, right 7th nerve weakness; bilateral optic atrophy; judgment and memory good	1	.....	..	.....
C. S.	32	Duration 9 mo.; recent progression with transient bulbar symptoms Bilateral pyramidal tract, cerebellar, and posterior column involvement; retrobulbar optic neuritis, O. D.; memory and judgment impaired; aggressive; uncooperative	3	Abnormal: very slow; left anterior temporal focus during hyperventilation	4	Moderate organic brain damage, Grade 4
H. H.	37	Duration 10 yr.; recent exacerbation Bilateral pyramidal tract and cerebellar involvement; optic atrophy, bilateral; posterior column involvement; memory good; judgment impaired	3	Abnormal: diffuse, mildly fast	1	Slight organic brain damage, Grade 2

J. S.	47	Duration 16 yr.; no recent exacerbation Spastic paraplegia; cerebellar signs; speech slurred; extreme emotional lability; memory and judgment impaired	4	Normal	0	Extensive organic brain damage, Grade 5
F. K.	43	Duration 8 yr.; no recent exacerbation Spastic paraparesis; cerebellar signs; bilateral optic atrophy; emotional lability; memory good; judgment poor	2	Normal	0	Extensive organic brain damage, Grade 5
E. J.	51	Duration 11 yr.; no recent exacerbation Spastic paraplegia; cerebellar signs; incontinence; emotional instability; judgment poor; memory good	4	Normal	0	Extensive organic brain damage, Grade 5
J. S.	50	Duration 10 yr.; no recent exacerbation Pyramidal tract and posterior column signs; optic atrophy, mild; judgment and memory abnormal	2	Multiple artifacts; could not be evaluated	..	Moderate organic brain damage, Grade 3
A. Y.	45	Duration 20 yr.; recent gradual progression Pyramidal tract, cerebellar, and bulbar involvement; optic atrophy, mild; euphoria; memory and judgment abnormal	3	Abnormal: irregular slowing and left temporal focus	2	Extensive organic brain damage, Grade 5
B. C.	39	Duration 17 yr.; no recent exacerbation Pyramidal tract, cerebellar, posterior column signs; optic atrophy, bilateral; incontinence; emotional lability; memory good; judgment fair	3	Normal	0	Moderate organic brain damage, Grade 3
R. S.	36	Duration 11 yr.; no recent exacerbation Spastic quadriparesis; optic atrophy; bulbar signs; cerebellar signs; memory and judgment impaired	5	Abnormal: diffuse, mildly slow	1	Moderate organic brain damage, Grade 3
I. C.	48	Duration 18 yr.; no recent exacerbation Moderate spastic paraparesis and cerebellar signs; memory and judgment normal	2	Normal	0	Moderate organic brain damage, Grade 3
A. G.	41	Duration 8 yr.; mild recent progression Spastic paraparesis, cerebellar and posterior column signs; emotional lability; memory normal; judgment impaired	4	Abnormal: amplitude asymmetry, left	2	Slight organic brain damage, Grade 2
C. S.	60	Duration 25 yr.; no recent exacerbation Mild pyramidal tract and cerebellar signs; mild memory and judgment defects	1	Normal	0	Slight organic brain damage, Grade 2

or moderately fast activity; 4, moderately slow or fast activity plus focal signs; 5, diffuse very slow or very fast activity, or paroxysmal activity, and 6, very slow or very fast activity plus focal signs.

The Rorschach ink blot test was used to detect the presence and extent of organic damage to the brain. The procedure for administering the test adhered to the standard practice of free association to all the 10 blots, followed first by a "nondirective" inquiry, to gain additional information on the subject's previous responses, and then by a probing period, to delineate further the areas and determinants incorporated in the perceptions given and to test the limits of the subject's capacities. The records were analyzed with an effort to grade the impairment of the variables involved. The degree of involvement was then artificially quantitated according to a numerical score which ranged from 0 (no indications of organic impairment) to 6 (severe organic impairment).

The metabolic studies, electroencephalographic recordings, and psychodiagnostic tests were performed and the results graded by independent observers, each observer, therefore, being unaware of and unprejudiced by the results of the others.

Values for cerebral oxygen consumption, cerebral glucose consumption, cerebral vascular resistance, and respiratory quotient were calculated in the usual way.[4]

RESULTS

A summary of clinical findings, electroencephalographic tracings, and results of psychodiagnostic tests is given in Table 1. The patients were graded clinically on the extent and severity of neurologic involvement and disability in an arbitrary comparative scale from 1 (least involvement) to 5 (severest involvement). These figures are recorded in the column on clinical data.

The cerebral circulatory and metabolic data are given in detail in Table 2. These are compared with values obtained from 20 normal subjects ranging in age from 26 to 52, with a mean age of 38. The ages of patients with multiple sclerosis ranged from 30 to 60, with a mean of 42, these patients falling into about the same age group as did the control subjects. The mean values for cerebral blood flow, arterial-cerebral venous oxygen difference, cerebral oxygen consumption, mean arterial pressure, and cerebral vascular resistance in the patients with multiple sclerosis did not differ significantly from the corresponding values for the normal controls. The mean values for arterial oxygen tension and saturation, arterial carbon dioxide content and tension, and arterial and cerebral venous pH also did not differ significantly from the normal expected values for subjects who are inactive and partially confined to bed. None of the patients had significant anemia. The mean respiratory quotient was about the same as that previously reported for normal subjects,[10] as are the mean values for arterial-cerebral venous glucose difference and cerebral glucose consumption.[3]

After the inhalation of 5% carbon dioxide and 95% oxygen by nine subjects, there was a rapid and consistent decrease in arterial-cerebral venous oxygen difference to values less than 50% of the initial level, denoting marked cerebral vasodilatation and indicating the responsiveness of the cerebral vessels of these patients to a known cerebral vasodilating agent.

Five of the 12 electroencephalograms were considered abnormal, though there was no consistency of pattern. The Rorschach ink-blot tests were considered to show evidences of organic brain damage in all 12 subjects on whom it was performed, and all but 2 showed evidence of moderate to severe damage. There

10. Schmidt and Kety, footnotes 4 and 5.

TABLE 2.—*Cerebral Circulatory and Metabolic Functions in Multiple Sclerosis*

Patient	Cerebral Blood Flow, Ml./Min./100 Gm. Brain	Arterial Oxygen Content, Vol. %	Venous Oxygen Content, Vol. %	Arterial Venous Oxygen Difference, Vol. %	Arterial Oxygen Tension, Mm. Hg	Venous Oxygen Tension, Mm. Hg	Arterial Oxygen Saturation, %	Cerebral Oxygen Consumption Ml./Min./100 Gm. Brain	Arterial CO_2 Content, Vol. %	Arterial pH	Venous pH	Arterial CO_2 Tension, Mm. Hg	Respiratory Quotient	Arterial-Venous Glucose Difference, Mg./100 Cc.	Cerebral Glucose Consumption Mg./Min./100 Gm. Brain	Glucose: Oxygen Ratio	Mean Arterial Pressure, Mm. Hg	Cerebral Vascular Resistance, Mm. Hg/Ml./Min./100 Gm. Brain
W. H.	59	18.3	12.1	6.2	..	33	96	3.7	.....	.....	.....	..	.....	.....	.....	.....	85	1.44
C. S.	58	18.6	13.0	5.6	..	34	94	3.2	.....	.....	.....	..	.....	.....	.....	.....	137	2.36
M. W.	58	18.7	12.3	6.4	..	33	97	3.7	.....	.....	.....	..	.....	.....	.....	.....	91	1.57
P. G.	59	18.6	10.9	7.6	..	30	98	4.5	.....	.....	.....	..	.....	.....	.....	.....	85	1.44
V. C.	55	19.2	13.5	5.7	..	35	96	3.1	.....	.....	.....	..	.....	.....	.....	.....	93	1.69
E. McD.	71	18.9	13.1	5.9	..	35	96	4.2	.....	.....	.....	..	.....	.....	.....	.....	89	1.25
C. W.	56	17.1	9.1	8.0	..	27	97	4.5	.....	.....	.....	..	.....	.....	.....	.....	92	1.64
W. S.	49	18.1	13.0	5.1	82	34	95	2.5	46.6	7.39	7.33	38	.....	.....	.....	.....	92	1.88
C. S.	70	17.2	12.5	4.7	79	39	94	3.3	49.8	7.37	7.33	44	0.90	8.0	5.6	1.67	92	1.53
H. H.	42	19.2	11.8	7.4	69	29	92	3.1	40.9	7.42	7.36	34	0.95	8.8	3.7	1.19	89	2.12
J. S.	80	18.1	11.7	6.4	102	37	97	5.1	43.3	7.36	7.30	40	1.05	10.8	8.6	1.69	92	1.15
F. K.	57	19.2	12.1	7.2	78	33	94	4.1	44.9	7.37	7.33	40	0.99	9.2	5.2	1.28	106	1.86
E. J.	64	14.5	9.2	5.3	102	34	97	3.4	48.0	7.37	7.33	43	0.94	6.2	4.0	1.17	82	1.28
J. S.	36	17.8	12.1	5.7	78	36	94	2.0	39.3	7.36	7.32	36	0.93	8.9	3.2	1.56	53	2.39
A. Y.	68	16.7	9.6	7.1	81	32	95	4.8	45.2	7.35	7.29	42	0.91	9.7	6.6	1.37	89	1.31
B. C.	51	15.4	8.0	7.4	98	31	96	3.8	42.2	7.33	7.26	38	0.92	11.9	6.1	1.61	86	1.68
R. S.	44	17.8	10.2	7.7	88	33	96	3.4	47.4	7.37	7.30	42	0.91	10.3	4.5	1.34	82	1.86
I. C.	60	14.8	7.6	7.2	108	30	97	4.3	47.6	7.35	7.28	44	.....	7.7	6.2	1.07	73	1.22
A. G.	45	18.1	10.6	7.5	85	32	95	3.4	50.2	7.37	7.31	44	0.84	10.7	4.8	1.43	99	2.20
C. S.	52	18.1	13.2	6.0	86	41	95	3.1	49.8	7.34	7.30	47	0.87	6.1	3.2	1.24	91	1.75
Mean	56.7	17.7	11.3	6.51	88	33	95.6	3.66	46.3	7.37	7.31	40.9	0.93	9.2	5.2	1.41	91.6	1.68
Standard Error	2.3	0.3	0.5	0.2	2.8	0.71	0.4	0.17	0.99	0.006	0.007	1.3	0.01	0.5	0.4	0.06	2.7	0.08
Control	62.9	.....	.....	6.27	..	..	..	3.90	.....	.....	.....	..	.....	.....	.....	.....	90.4	1.47
P value	> 0.5	.....	.....	>0.5	..	..	..	>0.2	.....	.....	.....	..	.....	.....	.....	.....	> 0.5	> 0.2

seemed to be general involvement of all the areas of organic influence tested, namely, perceptual processes, conceptual processes, imaginative processes, emotionality, memory, and verbal reactions to the test stimuli.

COMMENT

The data presented here indicate that there is no alteration in any of the measured cerebral circulatory or metabolic functions in multiple sclerosis. There is no correlation between clinical severity of the disease and cerebral blood flow, cerebral metabolism, or cerebral vascular resistance; nor is there any evidence of correlation between clinical exacerbation or progression of the disease and these measured functions. The discrepancy between these results and those reported by Tucker, Donald, and Farmer [11] cannot be explained.

It is recognized that this means of measuring cerebral blood flow and cerebral metabolism is relatively crude and is probably not capable of measuring small, localized areas of vascular spasm or thrombosis which might conceivably be mechanically responsible for the lesions of multiple sclerosis. On the other hand, one would expect some indication of involvement of cerebral vessels in a group of this size and with disease of such clinical severity if vascular spasm or thrombosis had an important causative relation to the pathologic lesions of the disease. In particular, the failure of the cerebral blood flow or vascular resistance to be altered from normal during exacerbation or progression of the disease, as indicated by this study, casts doubt on the credibility of the hypothesis that vascular spasm or thrombosis may be related to the pathogenesis of the lesions of multiple sclerosis. The normal responsiveness of the cerebral vessels of these patients to inhalation of carbon dioxide is additional evidence for the absence of widespread cerebral vascular thromboses in these patients, although small, localized areas of thrombosis would probably not be detected by this method.

The finding that cerebral oxygen and glucose consumption are normal in patients with multiple sclerosis is surprising in view of the widespread damage observed pathologically in these patients. Several possible explanations suggest themselves: 1. Anatomically, the distribution of cerebral lesions in multiple sclerosis is more pronounced in the brain stem, a region which probably contributes much less to the total measured metabolism of the brain than do the relatively uninvolved cerebral hemispheres; hence impairment of metabolism in the brain-stem area would have a relatively small effect on total cerebral metabolism. 2. Histologically, the lesions of multiple sclerosis involve mainly the myelin sheaths, with relative sparing of tissues of high metabolism, such as axis-cylinders and nerve cells, thus accounting for apparent absence of reduction in total cerebral metabolism. 3. The alterations of tissue metabolism in multiple sclerosis may be much more discrete than were measured here, involving changes in lactate and pyruvate metabolism, or even finer changes in cellular enzymatic processes. 4. The extent of tissue destruction in multiple sclerosis may be sufficiently severe that many of these areas of destruction are nonviable and are thereby excluded from the circulation, and would not participate in the total cerebral metabolism as measured by the nitrous oxide technique. Other explanations present themselves, but these appear to be the most likely on the basis of available evidence.

11. Tucker, W. M.; Donald, D. C., Jr., and Farmer, R. A.: Cerebral Blood Flow in Multiple Sclerosis, A. Res. Nerv. & Ment. Dis., Proc. (1948) **28**:203, 1950.

Although there was no correlation between the type of localization of electroencephalographic abnormality and the site or extent of lesions as determined by clinical examination, it is of interest that all the patients whose disease was in clinical exacerbation and who had electroencephalograms made had abnormal tracings. This finding is in qualitative agreement with the data of Jasper, Bickford, and Magnus,[12] who observed a correlation between the acuteness of the pathologic process in multiple sclerosis and the severity of the electroencephalographic abnormality. Our study revealed complete absence of correlation between electroencephalographic findings and measured cerebral circulatory and metabolic functions, and between the electroencephalographic pattern and evidences of organic impairment as measured by psychodiagnostic testing. An explanation of these disparities is not available, and further observations which may serve to correlate electroencephalographic patterns with changes in cerebral metabolism are needed. In this study measurements of cerebral metabolism do not reveal any basis for the electroencephalographic abnormalities or for the pronounced alterations in the results of psychodiagnostic testing.

It would seem that the Rorschach ink blot test is much more sensitive in its ability to detect organic damage to the brain than either the electroencephalogram or the nitrous oxide procedure. There was no correlation between the severity of involvement as indicated by psychodiagnostic testing and severity as indicated by clinical examination, stage of the disease, measured cerebral metabolism, or electroencephalographic changes.

SUMMARY AND CONCLUSIONS

Cerebral blood flow and cerebral metabolism were measured by the nitrous oxide technique in 20 patients with multiple sclerosis in various stages of the disease, and electroencephalographic recording and Rorschach ink blot tests were performed on 12 of these patients. There was no change from normal in any of the measured cerebral metabolic functions or evidence that exacerbation of the disease affected the cerebral blood flow or metabolism, though the electroencephalogram was abnormal in all patients with exacerbation of the disease. It is felt that these studies cast doubt on hypotheses which incriminate vascular spasm or thrombosis as a mechanism responsible for the pathologic lesions of multiple sclerosis. Several explanations are offered for the observation that cerebral oxygen and glucose consumption are apparently unaffected by this disease.

No correlations were observed among clinical findings, measured cerebral metabolic functions, electroencephalograms, and results of psychodiagnostic testing. The Rorschach ink blot test seemed to be much more sensitive in detecting the presence and extent of organic damage to the brain than the nitrous oxide technique or the electroencephalogram.

Mrs. Janet Fetner gave technical assistance.

12. Jasper, H.; Bickford, R., and Magnus, O.: The Electro-Encephalogram in Multiple Sclerosis, A. Res. Nerv. & Ment. Dis., Proc. (1948) **28**:421, 1950.

GLUTAMINE, GLUTAMIC ACID, AND γ-AMINOBUTYRIC ACID IN CEREBROSPINAL FLUIDS

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THE ROLES of glutamic acid and its derivatives glutamine and γ-aminobutyric acid, which are present in nerve tissue in appreciable quantities, are poorly understood.[1] It is possible that the concentrations of these compounds in cerebrospinal fluid may reflect changes in nerve tissue metabolism resulting from neurological disorders. Since available data are scanty,[2] it seemed worth while to determine the concentrations of glutamic acid and related compounds in the cerebrospinal fluid in a group of patients with various types of neurological disorders.

METHODS AND MATERIAL

Specimens of cerebrospinal fluid were obtained from patients in the University of Virginia Hospital undergoing pneumoencephalograms for diagnosis. Each specimen was contrifuged for removal of cellular debris and, whenever possible, was analyzed immediately for glutamic acid and glutamine. It was determined that the values obtained were not changed after overnight storage at 5 C.

Glutamic acid and glutamine were determined by the procedures recommended by Krebs,[3] which utilize the enzymes in Clostridium welchii (per fringens) for deamination of glutamine and decarboxylation of glutamic acid. Cl. welchii (strain SR-12) was grown in a medium used by Meister, Sober, and Tice.[4] The organisms were harvested and lyophilized, and 15 mg. of the dried material was used with 3.5 ml. of cerebrospinal fluid. The Warburg manometric procedure was used for determining the carbon dioxide, and the Archibald [5] technique, utilizing vacuum distillation and Nesslerization, was employed for estimating ammonia. In order that the best performance of the distillation apparatus should be insured,[6] it was found necessary to pass air continuously through the capillary to avoid clogging. All samples were analyzed in triplicate. With these procedures, both CO_2 and NH_3 could be analyzed with an accuracy of about 5%.

From the Department of Biochemistry, University of Virginia Department of Medicine.
This investigation was supported by Research Contract V1001M-1074, Veterans Administration.

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The paper chromatography technique of Dent[7] was used for identifying γ-amino butyric acid. Twenty milliliters of an ultrafiltrate of cerebrospinal fluid[8] was desalted[9] and evaporated *in vacuo*. The residue was dissolved in 1 ml. H_2O and 30 μl. was applied to the filter paper for analysis. A few samples of concentrated cerebrospinal fluid were analyzed by the chromatographic technique of Moore and Stein,[10] in which ultrafiltrates of cerebrospinal fluid were evaporated to dryness *in vacuo* and dissolved in a small amount of water. An aliquot equivalent to 20 ml. of cerebrospinal fluid was added to the adsorption column, and the eluate of the first 225 ml. was analyzed for amino acids.

RESULTS AND COMMENT

The values for glutamine in 26 cerebrospinal fluids varied from 5.4 to 9.4 mg. per 100 cc., with a mean value of 7.35 mg. and a standard error of ± 2.0 mg., per

Concentration of Glutamine and Glutamic Acid in Cerebrospinal Fluids of Patients

Glutamine, Mg./100 Cc.	Glutamic Acid, Mg./100 Cc.	Diagnosis
5.4	....	Cerebellopontine angle tumor
5.8	— 0.1	Jacksonian epilepsy
6.0	— 0.4	Depressed fracture of skull
6.3	....	Convulsions, no diagnosis
6.5	— 0.7	Cerebrodegenerative process
6.6	+ 0.2	Jacksonian epilepsy
6.7	+ 0.2	Focal epilepsy
7.0	....	Convulsions, no diagnosis
7.1	— 0.9	Generalized convulsive seizures, cause undetermined
7.1	....	Epilepsy
7.1	....	Epilepsy, psychomotor
7.1	....	Psychoneurosis
7.1	....	Diffuse cerebral toxic degeneration
7.2	....	No diagnosis
7.3	— 0.1	Arteriovenous fistula, right frontal lobe
7.3	— 0.2	Paranoid psychosis
7.5	....	No diagnosis
7.6	....	Involutional psychotic reaction
7.7	— 0.5	Motor aphasia
8.0	....	Epilepsy, grand mal
8.1	....	Systic hemangioblastoma, cerebellum
8.7	+ 0.8	Medulloblastoma
8.8	+ 0.1	No diagnosis
8.8	....	Convulsions, no diagnosis
8.9	0.0	Pinealoma
9.4	— 0.9	No diagnosis

100 cc. (Table). These results are in agreement with the values of Richter and associates,[28] who reported a range of 6.9 to 8.6 mg. per 100 cc. of glutamine in the spinal fluids of eight schizophrenic patients.

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9. Consden, R.; Gordon, A. H., and Martin, A. T. P.: Identification of Lower Peptides in Complex Mixtures, Biochem. J. **41**:590-596, 1947.

10. Moore, S., and Stein, W. H.: Chromatography of Amino Acids on Sulfonated Polystyrene Resins, J. Biol. Chem. **192**:663-681, 1951.

The data for the glutamic acid in 13 cerebrospinal fluids indicated that only traces of this amino acid may be present. The significance of the small amount (0.8 mg. per 100 cc.) in one case is not clear. The majority of these values are negative and probably reflect the limitations of the analytical procedures. Pond [2b] noted the presence of glutamic acid in spinal fluids by using the paper chromatography procedure. This observation could be confirmed and may be explained by the partial decomposition of glutamine during the various steps which involve desalting and chromatography.

The fluids, analyzed qualitatively by the procedure of Stein and Moore, showed a pronounced peak in the serine-asparagine area. It could be shown that this was due to glutamine, since hydrolysis of the fluids with acid caused this peak to disappear and a new peak was observed in the glutamic acid area. Similar changes were noted before and after hydrolysis of a glutamine solution.

γ-Aminobutyric acid could not be detected in cerebrospinal fluid by paper chromatography. The amino acids observed were the same as those described by Pond.[2b]

SUMMARY

The glutamine concentration of cerebrospinal fluid in patients with a variety of neurological disorders was found to have a mean value of 7.35 ± 2.0 mg. per 100 cc. No relation could be established between glutamine concentration and the type of disorder. Glutamic acid was either absent or present only in traces. γ-Aminobutyric acid could not be detected in any of the fluids investigated.

Mr. Wade Fleenor gave technical assistance.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

CEREBRAL AREA ESSENTIAL TO CONSCIOUSNESS. G. N. THOMPSON, Bull. Los Angeles Neurol. Soc. **16**:311 (Dec.) 1951.

Thompson reports nine cases of impairment of consciousness. In six of the cases the impairment of consciousness was that of a lethargic stupor from which the patient could be partially aroused. Analysis of these six cases showed that in five there was a bilateral lesion of the thalamus. In the sixth case there was a hypothalamic lesion. In three cases there was deep coma and the patients failed to respond to any stimulus. In these three cases the lesions involved the mesencephalic-hypothalamic junction. A tenth case, in which there was no impairment of consciousness, is described; in this case the lesion was one of complete destruction of the pons with extension into the mesencephalon.

Thompson concludes from these case studies that bilateral thalamic and hypothalamic lesions result in impairment of consciousness to the degree of a lethargic stupor from which the patient can be partially aroused. Either a bilateral thalamic lesion alone or a hypothalamic lesion alone may produce this syndrome. The depth of stupor does not seem to depend upon the extent of involvement of these structures. Lesions of the junction of the hypothalamus and of the subthalamus with the mesencephalon result in deep coma, from which no degree of recovery is possible. Both the stupor and the coma are permanent and irreversible. Thompson concludes that the engram system essential to crude consciousness is located where the mesencephalon, subthalamus, and hypothalamus meet. Pathologic sleep or stupor may result from lesions just above this area, in either the hypothalamus or the thalamus, if the lesion is bilateral.

ALPERS, Philadelphia.

PROCAINE BLOCK OF FRONTAL LOBE WHITE FIBERS AS A MEANS OF PREDICTING THE EFFECT OF PREFRONTAL LOBOTOMY: II. CLINICAL EVALUATION. W. P. VAN WAGENEN and C. T. LIU, J. Neurosurg. **9**:30, 1952.

The patients selected for procaine block in this study were divided into a psychotic (21 patients) and a nonpsychotic group (6 patients). Members of the former group were all severely disturbed patients who had all been passed by the lobotomy board as suitable for lobotomy according to rigid standards set up by a national board. The nonpsychotic group were those selected from a neurosurgical practice because of severe, disabling hypochondriasis, complaints of pain, or of nursing problems.

The authors' usual technique is to make two small burr holes, with the use of local anesthesia if possible, over the frontal poles of the brain, or just anterior to the coronal suture bilaterally. A 2% solution of procaine hydrochloride, 3 cc. on each side, is injected very slowly with an extremely fine needle. The procedure and results in each of the 27 cases are detailed.

From their results, Van Wagenen and Liu conclude that procaine injections into the white fibers of the frontal lobes of the brain may be used as an aid in predicting the effect of a prefrontal lobotomy upon the behavior of a psychotic patient. It will not aid in predicting the final course of the psychosis. This procedure is most useful in predicting relief from unusual pain by a prefrontal lobotomy.

It was found that procainization is most reliable when done in psychotic patients during their period of overactivity. The observed effects upon behavior after procainization follow the effects of lobotomy in two of three cases.

ALPERS, Philadelphia.

Meninges and Blood Vessels

CARCINOMATOSIS OF THE LEPTOMENINGES. L. L. JACOBS and K. J. RICHLAND, Bull. Los Angeles Neurol. Soc. **16**:335 (Dec.) 1951.

Jacobs and Richland report the cases of four patients with primary carcinomatosis of the cranial leptomeninges—one with a proved primary carcinoma of the stomach, the second with supposed origin in the gastrointestinal tract, the third with no primary neoplasm found elsewhere in the body, and the fourth with a known carcinoma of the breast with metastases to the regional lymph nodes. The cases of this disease which have previously been reported are analyzed.

When the cancer cells invade the leptomeninges diffusely, one of several clinical syndromes may develop, depending upon whether the subarachnoid infiltration is widespread or localized and on the depth of parenchymal penetration by way of the perivascular spaces. These clinical manifestations are those suggestive of (1) meningeal irritation, (2) increased intracranial pressure (nonabsorptive type), (3) multiple cranial nerve paralyses, and (4) the so-called organic mental syndrome. In any given case, varying degrees of combinations of these typical syndromes may be produced, including involvement at the spinal cord level. The authors feel that for any adult with chronic meningeal signs of obscure origin, or persistent intracranial pressure without localization ("pseudotumor cerebri"), one should consider the diagnosis of carcinoma of the leptomeninges and investigate carefully the possibility of a primary neoplasm elsewhere in the body, particularly in the gastrointestinal tract.

From their own experience and in the cases reported in the literature, the authors found no instances in which there was evidence of perivascular parenchymal involvement without leptomeningeal infiltration. In the lesions they studied microscopically, the perivascular involvement was consistently greater in the superficial layers of the cortex. They therefore propose that the initial invasion in diffuse leptomeningeal involvement, when it occurs without gross nodule formation, must begin in the meninges. The mode of possible spread is discussed.

On the basis of the data here studied, the authors conclude that when gastrointestinal carcinomas metastasize to intracranial structures they tend to lodge in the leptomeninges rather than within the nerve tissue. This seems to be characteristic of malignant growths of the gastrointestinal tract, although carcinomas from other sources may also metastasize to the leptomeninges. In many instances the source of the primary malignant growth escaped detection, but even in the majority of these cases the gastrointestinal tract was suspect, a conclusion based on the appearance of the cancer cells and their architectural arrangement. Thus, the predominant source of carcinomatosis of the leptomeninges is the stomach, less often the bowel.

ALPERS, Philadelphia.

Diseases of the Brain

RESULTS OF EXPLORATION IN PATIENTS WITH CLINICAL DIAGNOSIS OF SUBDURAL HEMATOMA. P. S. BERGMAN, M. NATHANSON, and E. D. FRIEDMAN, J. A. M. A. **149**:1529 (Aug. 23) 1952.

The medical literature contains many descriptions of the clinical features and operative findings in proved cases of subdural hematoma. Little attention has been directed to cases in which a subdural hematoma was suspected clinically but was not found at operation. The authors' purpose in this report is to compare two such groups in order to evaluate better the diagnostic and prognostic features of this clinical entity.

One hundred consecutive cases of suspected subdural hematoma, occurring during a three-year period, were reviewed. A comparison was made of two groups, 67 patients who had subdural hematoma and 33 who did not.

It was found that no reliable clinical features distinguished the two groups. When the authors used as criteria the combination of head injury, changes in consciousness, and failure to improve, the suspected diagnosis proved correct in 68% of the series.

Neurological signs, such as pupillary changes, aphasia, and hemiparesis, did not occur with sufficient frequency to be reliable. Reliance could not be placed on lateralizing signs in view of the frequency of their occurrence in the group of patients without subdural hematoma. The

number of hematomas which are proved to be bilateral or on the unsuspected side justifies the practice of performing bilateral trephination in every case. In this series electroencephalography was of no value in differentiating patients with subdural hematoma from those who had head injuries without subdural hematoma.

Bergman and his colleagues point out that the prognosis after successful removal of a subdural hematoma should always be guarded. In this series the number of deaths among the patients without subdural hematoma was proportionally as high as in the patients with subdural hematoma. Also, there was little difference in the incidence of permanent disability in the two groups. It was felt that disease of the brain itself, whether or not it was due to injury, was probably the chief determinant of mortality and morbidity. ALPERS, Philadelphia.

Diseases of the Spinal Cord

POSTERIOR CERVICAL SYMPATHETIC SYNDROME OF BARRÉ-LIÉOU IN TRAUMATISM OF THE CERVICAL CORD. HENRI ROGER. Rev. oto-neuro-ophtal. **24**:32 (Jan. 1) 1952.

This syndrome is encountered most frequently with arthritis of the cervical portion of the spinal column and was described by Barré, in 1925, and his student Liéou, in a Strassburg thesis in 1928. Crusem, another student of Barré's, in 1932 pointed out the appearance of the syndrome following trauma. Roger, with Alliez and Paillas, called attention to the frequency of the Barré-Liéou syndrome in cervical injury. Trauma may be transmitted to the neck in head injury and may result from sudden hyperextension to the head, and even from sudden forced flexion of the head. In one of Roger's cases the accident was a fall in which the patient landed on his heels. The accident was sometimes so old that the patient did not recall it and was reminded of it only by questioning.

The syndrome is seen more frequently in older patients. The question of repeated mild traumatism, such as carrying loads on the neck repeatedly or the effect of pneumatic drills, is still not clear. Complaints usually do not appear immediately after the trauma. They come on a week, a month, or even a few years afterward. Headache is usually occipital, but may be frontal, and even intraocular. It usually radiates from the occipital region to the frontal but may radiate fronto-occipitally. Dizziness is usually mild and in the nature of transitory unsteadiness without attacks of vertigo. The patient usually does not fall. Ear noises are frequent. Transitory obscuration of vision sometimes appears. There are usually no objective signs. In one case the author encountered paresthesia of the pharynx. Facial pain with vasomotor changes is sometimes seen. In one case there was twitching of an upper lid. Roger notes the frequency of psychogenic superimposition-depression, difficulty in thinking, impaired memory, and anxiety.

Symptoms referable to the neck are important in diagnosis. The neck is often stiff; pain with motion and limitation of motion are not infrequent. Pain is induced by posterior extension and lateral flexion of the head. There is also occasional tenderness over the cervical region. Roentgenograms sometimes show fracture of the spine, and occasionally arthritic changes, which may come on a long time after the accident. Arthritic changes associated with the Barré-Liéou syndrome, according to Bartschi-Rochaix, are seen more frequently with lesions of the third to the fifth cervical than with lesions of the fifth to the sixth cervical vertebrae. Straightening of the cervical curve is often seen; herniated disk may also be present.

The syndrome often comes on insidiously and reaches a maximum intensity usually in a few weeks. It may be very recalcitrant to treatment. One of the author's patients had continued complaints for 10 years. It is oftenest confused with the postconcussion syndrome. Differential diagnosis is difficult. The postconcussion syndrome usually appears soon after the trauma and gradually diminishes in intensity, remaining at a certain level of intensity for a long time. The posterior sympathetic syndrome usually appears later, progresses over a longer period, and clears up less quickly. The author points out the necessity for more frequent examination of the neck in cases of head injuries. The disability in most cases is 20 to 25%. Heat and x-ray treatments are recommended. The author reports no necessity for surgical intervention in any of his cases. Relief of the Barré-Liéou syndrome has been reported after removal of a cervical disk.

N. SAVITSKY, New York.

Vegetative and Endocrine Systems

GARGOYLISM AND MORQUIO'S DISEASE. H. ZELLWEGER, L. GIACCAI, and S. FIRZLI, A. M. A. Am. J. Dis. Child. **84**:421 (Oct.) 1952.

The authors report three cases of lipochondrodystrophy (gargoylism; Hurler's syndrome). The fully developed syndrome is characterized by (1) epiphysial-metaphysial dysostosis, or dysostosis-desmosis, with stunted trunk, kyphosis, deformities of the sternum and ribs, short extremities, scaphocephaly, bulging forehead, claw hands; (2) signs of lipid or glucoprotein storage, with hepatosplenomegaly, corneal cloudiness, mental deterioration, abnormal granulations in the white blood cells and bone marrow, and (3) gruesome gargoyle facies, hypertrichosis, flabby skin, and umbilical hernia. Case 1 was previously reported as one of Léri's *pléonostéose*. At that time only slight mental retardation and some skeletal changes (short cranial base, distorted vertebral bodies, oar-shaped ribs, enlarged and cylindrical diaphyses) were present. At the time of the present report the patient manifests signs of "storage disease": progression of mental deterioration, hepatosplenomegaly, basophilic granules in the lymphocytes, and cloudy corneas. In the other two cases the patients, siblings aged 9 and 5 years, were of consanguineous parents. The former patient presented fully developed gargoylism; the latter had typical skeletal changes, but the only storage manifestations were very fine deposits in one cornea, seen only with the slit lamp, and abnormal granulations in leucocytes. Without knowledge of the older sibling, the condition would have been regarded as Morquio's disease (eccentro-osteochondrodysplasia). Thus, clouding of the cornea and granulations of the white blood cells may occur earlier than hepatosplenomegaly and signs of cerebral involvement. In cases of epiphysial-metaphysial dysostosis, the cornea should be examined with the slit lamp and the white cells examined for granules. The authors believe that in most cases the differential diagnosis of different types of epiphysial-metaphysial dysostosis based only on x-ray data is unreliable.

SIEKERT, Philadelphia.

Treatment, Neurosurgery

FATAL CONVULSIVE SEIZURES ASSOCIATED WITH CORTISONE THERAPY. L. J. GEPPERT, A. C. DIETRICK, E. H. JOHNSTON, and C. J. LIND, A. M. A. Am. J. Dis. Child. **84**:416 (Oct.) 1952.

A 5-year-old boy with rheumatoid arthritis was treated with 300 mg. of cortisone the first day, 200 mg. the second day, and 100 mg. daily thereafter. On the sixth day hypertension (blood pressure 140/100) developed. The dose was reduced to 50 mg. on the ninth day. On the 12th day, 24 hours after the last dose of cortisone, tremor of the right hand developed. The blood pressure was 160/100. Within an hour generalized convulsions occurred. The patient remained in coma and in a convulsive state from this time until his death, 14 days later. Chemical values of the blood were normal, except for a blood sugar of 316 mg. per 100 cc. soon after the onset of convulsions; a few hours later it was 94 mg. per 100 cc. and remained normal thereafter. The cerebrospinal fluid contained no cells, and the protein was 190 mg. per 100 cc. Barbiturates, calcium gluconate, and procaine failed to control the convulsion. The patient was practically decorticate, and an electroencephalogram showed a disorganized stupor record, with marked depression of cortical activity. Autopsy showed bronchopneumonia, but no pathologic change to account for the coma and convulsions. The brain showed only edema around an occasional intracerebral vessel. Electrolyte imbalance, water retention, cerebral edema, vasospasm, or hypertension, alone or in combination, did not seem responsible for the convulsions. The authors postulate a direct or an indirect effect of cortisone on the cerebral cortex.

SIEKERT, Philadelphia.

Encephalography, Ventriculography and Roentgenography

SECOND-DAY PNEUMOENCEPHALOGRAPHY. J. A. STEWART, Am. J. Roentgenol. **68**:749, 1952.

Stewart had the opportunity of studying routine encephalograms made on psychotic patients who had no known organic disease of the brain. These studies were done as a routine procedure

before prefrontal lobotomy. In addition, 15 studies were made on patients with a history of trauma, and 7 studies were done on patients with a history suggestive of organic disease of the brain. Anteroposterior, posteroanterior, and right lateral projections were taken with the patient in the upright position immediately after 105 cc. of air was injected into the spinal canal. Twenty-four hours later an identical set of roentgenograms was made with the patient in the same positions. Measurements were made on the posteroanterior film, according to the method of Schatzki, Baxter, and Troland (*New England J. Med.* **236**:419, 1947) for a comparison of the widths of the ventricles in the two examinations, made 24 hours apart. In this study Stewart used a standard target-film distance (33 in., or 84 cm.), standard positions, and a standard amount of air. However, he found that many errors occurred in the attempt to measure the ventricles. It was difficult to determine the proper points from which to measure, and there was a considerable human error in the study. For this reason, he computed the area of each ventricle as seen on the posteroanterior projection and compared the areas of the corresponding ventricles on the films made 24 hours apart. With respect both to the linear and to the area measurements, he was of the opinion that there was no statistical significance in the differences in size of the ventricles in the two sets of films. The arithmetical mean for the measurements suggested that the ventricles were slightly larger on the second day, but in many cases the reverse was true.

In all previous comparisons of the sizes of the ventricles on the first and second days, the patients had organic disease of the brain or suspected organic disease. Stewart believes that in the relatively normal brains of these psychotic people there is no significant difference in the sizes of the ventricles on succeeding days. However, he does believe that second-day pneumoencephalography is of value as a diagnostic aid because it has been shown to accentuate the roentgenographic demonstration of lesions of the brain which were questionable when the first roentgenograms were made.

WEILAND, Grove City, Pa.

UNILATERAL CALCIFICATIONS OF THE BASAL GANGLIA. S. A. TRUFANT and W. B. SEAMAN, Radiology **59**:521, 1952.

Trufant and Seaman report a case in which roentgenograms of the skull revealed an area of calcification in the region of the basal ganglia on the right side. The patient, a woman aged 33, had had stiffness in the fingers of the left hand, a rigid gait, and a drawing sensation in the left hand, the left leg, and the left side of the face for about 15 years. She had not lost the power to perform skilled tasks with either hand. For a few months preceding the examination she had had a few episodes of left-sided headaches and a tendency for the left corner of the mouth to be drawn laterally. Examination showed that the patient held the fingers of her left hand stiffly extended, although they could be flexed normally. There was some cogwheel rigidity at the left elbow. The left knee was somewhat rigid when the patient walked. The patient also had a psychoneurosis of long standing.

Roentgenograms were made of the skulls of the patient's sister and her two daughters, but no intracranial abnormalities were found.

WEILAND, Grove City, Pa.

RESULTS OF RADIATION THERAPY IN VASCULAR ANOMALIES OF THE CENTRAL NERVOUS SYSTEM. G. KAPLAN, B. ROSWIT, and E. G. KRUEGER, Radiology **59**:555, 1952.

The authors report nine cases of vascular malformations of the central nervous system, in all of which the treatment was first surgical, followed by x-ray therapy. In five of the nine cases the lesion was an arteriovenous angioma of the brain. In four of these it was observed surgically; in the fifth the diagnosis was made by means of cerebral angiography, and the common carotid artery was ligated before x-ray therapy was given. In the other four cases the lesion was a varix of the spinal cord. Surgical treatment consisted of decompression in all cases except the one in which ligation of the common carotid artery was the only surgical procedure. In one other case the carotid artery was ligated after surgical decompression.

The x-ray therapy varied considerably from case to case, both in quantity and in quality of radiation administered. The depth dose varied from 700 to 2,400 r in the series of nine cases. The total time of treatment also was extremely variable from case to case. The authors feel that no beneficial results were obtained from their x-ray therapy and that radiation has no role in management of vascular anomalies of the central nervous system.

WEILAND, Grove City, Pa.

News and Comment

CONGRESS OF NEUROLOGICAL SURGEONS

The third annual meeting of the Congress of Neurological Surgeons will be held at the Roosevelt Hotel, New Orleans, on Nov. 12, 13, and 14, 1953.

Sir Geoffrey Jefferson, Consulting Neurosurgeon, Manchester Royal Infirmary, Manchester, England, will be guest speaker. There will be panel discussions on the following subjects:

The Anatomy and Physiology of the Frontal Lobes
Psychosurgery: Indications and Sequelae
Use of Fluids and Electrolytes in the Management of the Neurological Patient

Further information may be obtained from Dr. Henry M. Suckle, 414 Tenney Building, Madison 3, Wis.

THE AMERICAN NEUROLOGICAL ASSOCIATION

At the Seventy-Eighth Annual Meeting of the American Neurological Association, held in Atlantic City, N. J., June 15-17, 1953, the following officers were elected for the year 1953-1954: president, Dr. Roland P. Mackay; president-elect, Dr. Percival Bailey; first vice-president, Dr. William G. Lennox; second vice-president, Dr. Russell Meyers; secretary-treasurer, Dr. H. Houston Merritt, and assistant secretary, Dr. Charles Rupp.

CHICAGO NEUROLOGICAL SOCIETY

At a meeting of the Chicago Neurological Society held on May 12, 1953, the following officers were elected for the coming year: Dr. Douglas N. Buchanan, president; Dr. Meyer Brown, vice-president; and Dr. Leo A. Kaplan, secretary and treasurer.

ILLINOIS PSYCHIATRIC SOCIETY

At the election of officers on May 27, 1953, the following members of the Illinois Psychiatric Society were elected to office: president, Dr. Alfred P. Bay, Manteno State Hospital, Manteno, Ill.; vice-president, Dr. H. H. Garner, Route 1, McHenry, Ill.; secretary-treasurer, Dr. Louis B. Shapiro, 664 No. Michigan Ave., Chicago 11; councilor, Dr. Jules H. Masserman, 8 So. Michigan Ave., Chicago 3; councilor, Dr. Helen McLean, 664 North Michigan Ave., Chicago 11.

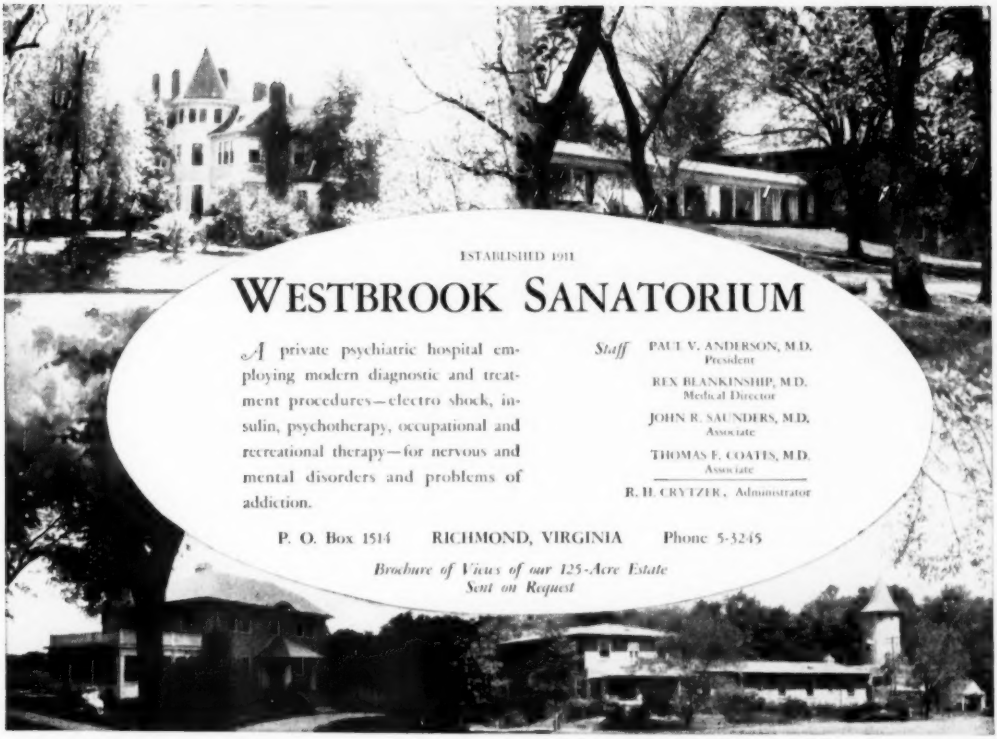
Books

Hemifacial Spasm. By Robert Wartenberg, M.D. Price, $4. Pp. 86. University Press, 114 5th Ave., New York 11.

This volume is a short monograph on a single affliction that occupies an unusually large space in the mind of the neurologist, the chief reason being that all there is about it appears on inspection; nothing beyond what is obvious is truly known. With his well-known thoroughness, the author advances the theory that hemifacial spasm is a nonpsychogenic, oftenest a cryptogenic, release phenomenon with the lesion in or above the facial nucleus, a disease, therefore, of the motor inhibitory apparatus. This book will be found valuable reading by those who cherish concise description and clear logic.

CORRECTION

In the article entitled "Electroencephalographic Findings Associated with Subdural Hematoma," by Dr. Ernst A. Rodin and his associates, published in the June, 1953, issue of the ARCHIVES, Dr. Bickford was incorrectly referred to as Mr. Bickford in the second footnote on page 743. On pages 750 and 751, the legend for Figure 1 should appear as the legend for Figure 3, and the legend for Figure 3, as the legend for Figure 1.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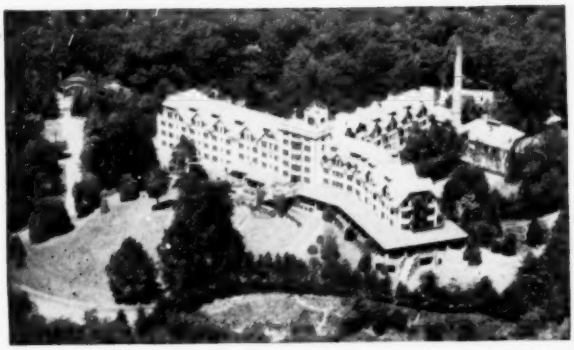

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